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Pharmacological Treatment of Dementia

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Structured Abstract

Context. Dementia is a chronic progressive disease with no known cure. It affects cognition, behavior/mood, physical functions and activities of daily living, and caregiver burden. Therapeutic interventions for dementia aim to affect these domains.

Objectives. To review the evidence and answer the questions: Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes? Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes? Are certain drugs, including alternative medicines (non-pharmaceutical), more effective than others? Do certain patient populations benefit more from pharmacotherapy than others? What is the evidence base for the treatment of ischemic vascular dementia (VaD)?

Data sources. Studies were identified by searching the Cochrane Central trial registry, MEDLINE® , PreMedline®, EMBASE, AMED, CINAHL®, Ageline, and PsycINFO.

Study selection. English-language randomized controlled trials were selected if they evaluated pharmacological agents for adults with a diagnosis of dementia according to the criteria of International Classification of Diseases (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM) or National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Crossover trials and studies with a quality score < 3 on the Jadad Scale were excluded.

Data extraction. Data were extracted on type of dementia, severity of disease, setting, regimen of pharmacological agents, study duration, main outcome measures, adverse effects, and results. The quality of studies was assessed, and the quality of adverse effect reporting was assessed. Effect sizes were calculated and data were pooled when appropriate.

Data synthesis. *(1) Efficacy:* One hundred and eighty-six Randomized Controlled Trials (RCTs) evaluated 97 drugs. As expected the findings varied with the dementia population and the specific outcomes in the various domains. Those pharmacological agents that showed a consistent effect of benefit are as follows: A) Global assessment was improved by donepezil, galantamine, rivastigmine, velnacrine, cerebrolysin and idebenone; B) Cognition (general and specific) was improved by donepezil, galantamine, metrifonate (this drug has been withdrawn from use in North America because of safety concerns), nicergoline, physostigmine, rivastigmine, velnacrine, memantine, cerebrolysin, ginkgo biloba, idebenone and propentofylline; C) Behavior/mood was improved by haloperidol; D) Quality of life/Activities of Daily Living (ADL) was improved by donepezil, galantamine and posatirelin. In general, caregiver burden and quality of life/ADL were not frequently evaluated. *(2) Delay disease:* Cerebrolysin, selegiline plus vitamin E, and donepezil showed some significant effects in delaying disease progress in patients with mild to moderate and moderately severe Alzheimer's disease. *(3) Head to head comparisons:* Superiority was seen for sulphomucopolysaccharides over CDP-choline, donepezil over vitamin E, antagonic-stress over nicergoline, antagonic-stress over meclofenoxate, posatirelin over citicoline, and pyritinol over hydergine. *(4) Patient populations:* Stratified analyses included: age, gender, Apolipoprotein E (APOE) genotype,

disease type, disease severity, race by location, care dependence, and presence of depression. Single populations of dementia subjects with Down's syndrome, and depression were evaluated. Evidence was inconclusive for this question. *(5) Ischemic VaD:* A total of 20 pharmacological interventions in 29 studies were applied to vascular dementias. Differences were suggested between multi-infarct dementia (MID) and Alzheimer's disease (AD) for 5′-MTHF-trazodone, AD and VaD for citalopram, and AD and MID for Ginkgo biloba. Trials with VaD patients showed effects for memantine, nicergoline, pentoxyfylline, idebenone, donepezil and cerebrolysin.

Conclusions. Pharmacotherapy for dementia can improve symptoms and outcomes. Adverse events should be more systematically reported. Few studies evaluated delay in either disease onset or progression, but there was some evidence suggesting delay in progression. Few studies compared drugs with other drugs. Due to poor evaluation, data was limited to consider efficacy of pharmacotherapy in different subgroups of patients. Some agents have been shown to be effective in VaD patients.

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Pharmacological Treatment of Dementia

Summary

Introduction

The focus of this review is the pharmacological treatment of dementia. Pharmacotherapy is often the central intervention used to improve symptoms or delay the progression of dementia syndromes. The available agents vary with respect to their therapeutic actions, and are supported by varying levels of evidence for efficacy. This report is a systematic evaluation of the evidence for pharmacological interventions for the treatment of dementia in the domains of cognition, global function, behavior/mood, quality of life/activities of daily living (ADL) and caregiver burden.

Many medications have been studied in dementia patients. These agents can be classified into three broad categories:

1. Cholinergic neurotransmitter modifying agents, such as acetylcholinesterase inhibitors.
2. Non-cholinergic neurotransmitters/ neuropeptide modifying agents.
3. Other pharmacological agents.

Although only five agents have been approved by the Food and Drug Administration (FDA) for the treatment of dementia, many other pharmacological agents have been evaluated in trials and may be prescribed in off-label use.

Given the range of pharmacological agents that have been tested in dementia, a systematic review of these interventions (using a consistent methodology) provides a meaningful contribution in this area. The key questions addressed in this systematic review are as follows:

1. Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?
2. Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?
3. Are certain drugs, including alternative medicines (non-pharmaceutical), more effective than others?
4. Do certain patient populations benefit more from pharmacotherapy than others?
5. What is the evidence base for the treatment of ischemic vascular dementia (VaD)?

This review considers different types of dementia populations (not just Alzheimer's Disease [AD]) in subjects from both community and institutional settings. The studies eligible in this systematic review were restricted to parallel RCTs of high methodological quality.

Methods

A team of content specialists was assembled from both international and local experts. The purpose of the expert panel was to assist in the topic assessment and refinement process; in addition, complex methodological issues were evaluated by this expert panel.

Search Strategy

Search strategies were developed and undertaken in the electronic databases including Cochrane Central, MEDLINE®, PreMEDLINE®, EMBASE, AMED, CINAHL®, AgeLine, and PsycINFO. In addition to the electronic databases, the bibliographies of retrieved papers were reviewed.

Eligibility Criteria:

Studies were included that met the following criteria:

- Populations included dementia patients who were 18 years or older in age.
- Diagnosis of dementia using criteria of International Classification of Diseases (ICD) 9 or 10, Diagnostic and Statistical Manual of Mental Disorders (DSM) III, III-R or IV, National Institute of Neurological and Communication Disorders and Stroke (NINCDS), Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), or Neurological and Communication Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN).
- Potential populations at high risk of dementia conversion in order to address the issue of delay in onset. These populations included: Mild Cognitive Impairment (MCI), Cognitive Impairment not Dementia (CIND), Cognitive Loss No Dementia (CLoND).
- Interventions were restricted to pharmacological agents, including food supplements (as defined by the FDA) administered for at least 1 day.
- Parallel design randomized control trials (RCT) in the English language of any sample size.
- Score of 3 or greater on the modified Jadad quality scale.

All types of instruments were considered for this review within the outcome domains.

Populations of dementias caused by toxic agents (e.g., alcohol) and temporary dementia (e.g., side effect of anesthesia) were excluded.

Data Collection and Reliability of Study Selection

All studies meeting eligibility criteria were reviewed to assess quality and data abstracted according to predetermined criteria. The articles were grouped according to the pharmacological agent used in the intervention. A team of study assistants were trained in the criteria for eligibility and quality for the purposes of this systematic review. Standardized forms and a guide explaining the criteria were developed from previous templates.

Study outcomes were classified into the following domains:

1. General cognitive function.
2. Specific cognitive function.
3. Global clinical assessment.
4. Behavior/mood.
5. Quality of life/ADL.
6. Effects on primary caregiver (also referred to as caregiver burden).
7. Safety as measured by the incidence of adverse effects (particularly serious events).
8. Acceptability of treatment as measured by withdrawal rate from trial due to side effects of the medication.

Measurement of Benefits and Harms

Evaluation of efficacy is based upon reported changes for outcomes in the principal domains of interest. Evaluation of the potential for harm is considered within three main areas: 1) the most frequently reported adverse events across studies for a specific drug, 2) the overall withdrawal rate due to adverse events for both the control and treatment groups, and 3) the range of frequencies reported for a subset of specific symptoms (nausea, diarrhea, dizziness, agitation, eating disorder) selected *a priori* and evaluated for all pharmacological interventions.

Measure of Effect Size and Meta-analysis

Effect sizes (ES) for trials were conducted for those pharmacological interventions with the same outcomes. In studies with multiple dosage groups and where sufficient data were provided, each dose level had an ES estimated separately relative to placebo. Before calculating a pooled effect size measure, the reasonableness of pooling was assessed on clinical and biological grounds, in terms of clinical homogeneity and therefore statistical meta-analysis was not appropriate for all outcomes or interventions.

Results

Question 1: Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?

Seventy-two studies examined cholinergic neurotransmitter modifying agents, 61 studies examined non-cholinergic neurotransmitter/neuropeptide modifying agents and 76 trials evaluated other agents used to treat dementia. Table 1 lists all the pharmacological agents and the number of trials (in brackets) eligible for review in this study. Twenty of these agents are detailed in this summary. All drug agents are detailed in the full report.

Summary of Cholinergic Neurotransmitter Modifying Agents

Carnitine. Six trials[1-6] evaluated carnitine in 925 subjects with mild to moderate severity, recruited predominately from the community. A dose of 2 to 3 g was compared to placebo for either 24 or 52 weeks.

Evidence of benefit is conflicting for the domains of general or specific cognition. Results were not statistically significant in any study but the lack of sufficient power may have influenced

these results. Similarly, no statistically significant differences were found in the domains of global assessment, behavior/mood, and quality of life/ADL. Statistical power could not be evaluated for the most of these outcomes.

Four of the six studies scored 3 for quality on reporting adverse events. Withdrawal rates due to adverse events varied from 0-3 percent (excluding results from one outlier trial[7]), and gastrointestinal symptoms were the most frequently reported types of adverse events.

Donepezil. Ten trials[8-17] in 3239 subjects evaluated the efficacy of donepezil compared to placebo, and one trial18 compared donepezil with vitamin E. Eight of the studies evaluated AD patients, for which at least half were recruited from the community (other studies did not specify). The subjects had predominately mild to moderate disease and doses of 5 or 10 mg were used with study duration from 12 to 56 weeks.

There is consistent evidence of benefit in the domains of general cognitive function and global assessment; the combined effect sizes for the Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-cog) and the Clinician's Interview-Based Impression of Change (CIBIC) were estimated. Based on the three studies that evaluated two different doses (5 and 10 mg), there was no consistent dose response relationship as the benefit was of similar magnitude for global assessment outcomes. Two of the three studies that evaluated behavior/mood outcomes, using the Neuropsychiatric Inventory (NPI), showed no statistically significant changes relative to placebo but these trials lacked sufficient power to detect a difference. There is evidence of benefit in ADL outcomes, although this outcome was evaluated by a variety of instruments. Caregiver burden outcomes were measured in a single study that did not report the findings for this domain.

Adverse events quality scores were 3 or greater for the majority of studies (n=7). Four trials provided evidence of a dose response for adverse events. One study showed a statistical difference for balance-related problems and asthenia (neurological fatigue) between placebo and treatment groups. Withdrawal due to adverse events ranged from 0–18 percent for treatment groups and 0–11 percent for placebo. Four out of 6 studies testing for differences between groups were statistically significant for diarrhea, nausea and vomiting.

Galantamine. Six trials1[9-24] in 3530 subjects compared the efficacy of galantamine with placebo. Doses of 24 and 32 mg were evaluated in half of these studies. Five studies evaluated only AD patients and there was limited information regarding the subjects' residence (community or institutional settings). All studies recruited subjects with mild to moderate disease and the drug was administered from 3 to 6 months duration.

Evidence of benefit is consistent in the domains of general cognitive function, global assessment and quality of life/ADL. Two of the three studies that evaluated behavior/ mood found statistically significant differences in favor of galantamine. A dose effect was evident in the ADL domain when comparing the pooled estimates of the Disability Assessment for Dementia (DAD); no dose effect was observed for outcomes in the global assessment domain, and this could not be evaluated for the general cognition domain. Caregiver burden was not evaluated in any trial.

Five of the six trials scored 3 out of 5 on our quality scale for rating adverse events. Withdrawal rates due to adverse events ranged from 4–9 percent for placebo and 8–27 percent for the treatment group. One study showed a dose response for adverse events. Although four trials did not report significance testing for differences between groups, two trials did report a statistically significant difference in weight loss between the placebo and treatment group. The most common adverse events were gastrointestinal symptoms (nausea and vomiting, diarrhea), eating disorders/weight loss, and dizziness.

Metrifonate. Nine studies[25-33] compared metrifonate to placebo in 2759 subjects with mild to moderate AD (the majority of studies did not specify community settings). Metrifonate doses from 50 to 80 mg were given for 21 days to 26 weeks duration.

All but one study showed metrifonate to have a consistent positive effect on measures of general cognitive function; none of the studies evaluated specific cognitive function measures. Effects on global assessment were less consistent but suggested a positive effect in four of the eight studies. Evidence for effect in the domains of behavior/mood and quality of life/ADL were not statistically significant in the majority of studies that evaluated these domains; however these were primarily evaluated as secondary outcomes and likely lacked sufficient power.

With the exception of a single study, quality scores for reporting adverse events were greater than 3. However, only one trial tested for differences between groups and found nausea and vomiting, diarrhea, and muscle and joint disorder to have statistically significantly differences. Withdrawal due to adverse events varied from 0–9 percent for placebo and 0–12 percent for the treatment group. It was difficult to determine which types of reported adverse events had the potential to cause serious harm. This is noteworthy as metrifonate has been withdrawn from use in North America, and Bayer has suspended Phase III trials,[34] because some patients in clinical

trials have experienced serious muscle weakness. This decision was based on the results of an experimental study showing risk of respiratory paralysis with the use of metrifonate. Other adverse events of concern included severe leg cramps, dyspepsia, and bradycardia. None of the studies that we reviewed indicated that if present, these events differed with statistical significance between groups. It is not clear if this inconsistency is a function of the methods used to collect and report adverse events, or a limitation of RCTs as a source of detecting serious adverse events when the incidence is low.

Nicergoline. Four trials[35-38] in 705 subjects compared nicergoline to placebo and one trial[39] compared it to a second drug (antagonic-stress) in mixed populations that included AD, Multi-Infarct Dementia (MID), Progressive Degenerative Dementia (PDD), Vascular Dementia (VaD), mixed dementia, and Senile Dementia of the Alzheimer's Type (SDAT), which were classified as mild to moderate in severity.

All placebo-controlled trials found a positive effect for general cognitive outcomes, but half the results were based on observed case (OC) analyses. The evidence for benefit was mixed in the domain of global assessments. No statistically significant differences were found for behavior/mood, nor quality of life/ADL outcomes but these were evaluated in few studies and as secondary outcomes (suggesting that sufficient power was an issue).

Quality scores for reporting adverse events varied from 2 to 5 for these four trials, and none tested for differences between groups. Withdrawal due to adverse events varied from 0–8 percent for placebo and 0–9 percent for the treatment group. With the exception of headache, which was reported in all four trials, it was difficult to determine which types of adverse events most characterized exposure to this pharmacological agent.

Physostigmine. Four studies[40-43] in 1198 subjects with mild to moderate AD evaluated physostigmine administered in patch and oral form (30 to 60 mg dose) from 6 to 24 weeks duration. All subjects were recruited from the community.

There is evidence that physostigmine has a statistically significant positive effect on general cognitive function, as three of the four studies showed improvement. Evidence for an effect on global function was mixed with no consistent effect. Similarly, for quality of life/ADL outcomes, all three studies that evaluated this domain showed no statistically significant difference but these were secondary outcomes and may reflect a lack of power. Behavior/ mood and caregiver burden outcomes were not tested.

The quality scores for reporting adverse events were generally low, scoring 1 or 2 out of 5. Withdrawal rates due to adverse events varied from 1–5 percent for placebo and 12–55 percent in the treatment group, with one study not reporting rates. The high withdrawal rates were in studies with sample sizes that varied from181 to 475 subjects. A single study tested for differences between groups, and found that dizziness, tremor, weight loss, asthenia, confusion, delirium, and respiratory problems (not detailed) were significantly different statistically. The cluster of reported types of adverse events suggests that gastrointestinal problems (abdominal pain, diarrhea, nausea and vomiting and eating disorder) were most frequently reported.

Posatirelin. Four trials[44-47] evaluated posatirelin in 931 subjects in a variety of mild to moderate dementia populations (AD, PDD, VaD) using 10 mg per day dose for 3 months duration.

Three of the four trials showed statistically significant improvement in general cognitive function and quality of life/ADL (as measured by Gottfries-Brane-Steen (GBS) subscales for these domains). The evidence remains inconsistent for benefit in global assessment (evaluated in only one trial) and behavior/mood (mixed results). Caregiver burden and specific cognitive function were not evaluated.

Quality scores for reporting adverse events varied from 2 to 4. Withdrawal rates due to adverse events ranged from 0–3 percent in placebo and 0–4 percent in the treatment group. None of the studies tested for statistically significant differences between groups for adverse events. At least three studies reported arrhythmia, nausea/vomiting, headache, rash/skin disorder, and sleep disorder.

Rivastigmine. Six studies[48-53] evaluated 2071 subjects with three of these studies limited to AD patients. Doses of rivastigmine varied from 1 to 12 mg, given for 14 to 26 weeks and only one study specified a community sample.

Evidence shows that general cognitive function improves with rivastigmine at dose of 12 mg but there are mixed results for efficacy at lower doses. Two trials evaluated specific cognitive function but the results were not consistent within studies (between general and specific measures); similarly, the results were not consistent for general and specific cognition between studies. There is consistent evidence of benefit for global function but the dosage at which this occurs has statistically significant variation among studies. In the domains of behavior/mood, quality of life/ADL, the findings were neither statistically significant nor consistent; most of these analyses were not based on intention to treat analysis and lack of sufficient power cannot be ruled out. Caregiver burden outcomes were not evaluated.

Quality scores for reporting adverse events varied from 2 to 5. Withdrawal rates due to adverse events ranged from 4–11

percent in the placebo and 11–27 percent in the treatment group. Two trials demonstrated a dose response; however, one of these trials showed statistically significant differences for nausea and vomiting only, and the other trial showed statistically significant differences for all the adverse events reported. The majority of studies reported dizziness, nausea and vomiting, eating disorder/weight loss, and headache. It should be noted that one study allowed intentional prescribed anti-emetic drugs to increase the tolerance of subjects taking rivastigmine.

Tacrine. Six studies[54-59] evaluated tacrine in 994 subjects predominately with mild to moderate AD at doses of 80 to 160 mg lasting from either 12/13 or 30/36 weeks in duration. Two other studies[60,61] involving 425 patients were non-placebo controlled studies. The majority of studies recruited community-based subjects.

A single trial showed benefit for general cognitive function. The small effect size was based on a series of related publications. The five trials showing no benefit for general cognitive function comprised small sample sizes and much shorter study duration. Thus, the evidence for benefit in general cognitive function is limited to a single trial. There is evidence for benefit in global function in two of the three trials. Changes in behavior/mood, quality of life/ADL domains, specific cognitive function, and caregiver burden were all not statistically significant, but lack of sufficient power cannot be ruled out.

The quality scores for reporting adverse events varied from 1 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0–12 percent for placebo and 0– 55 percent in the treatment group. The higher rates of withdrawal were associated with higher doses. Elevated alanine transaminase (ALT) or hepatic abnormality (placebo=4–13 percent, all doses tacrine=7–67 percent) was reported in six studies, raising concerns for the potential for serious liver damage. None of these trials tested for differences between treatment and placebo with respect to adverse events. Five studies reported nausea and vomiting, gastrointestinal problems, and dizziness. There is evidence for potentially serious adverse events associated with liver dysfunction in six trials.

Velnacrine. Three studies[62-64] evaluated the effects of velnacrine in 774 AD patients with a probable severity classification. Doses between 75 mg twice daily and 225 mg were given for 15 to 24 weeks duration. Location of recruitment was not specified.

Statistically significant positive effects were observed for general cognitive function, and global assessment in the two studies with sample sizes over 300 subjects. Behavior/mood and caregiver burden showed some benefit in one trial[62] at the highest dose only. Quality of life/ADL was tested as a secondary outcome and showed mixed findings.

Quality scores for reporting adverse events were 3 for all studies. Withdrawal rates varied from 0–22 percent for the placebo group and 5–33 percent for the treatment group. None of the studies reported a dose response. None of the studies tested for statistical differences between the placebo and treatment groups. Two studies reported aberrant hematology and hepatic abnormality[62,64]; for these two studies the rates of occurrence were 2–21 percent for placebo, and 32–40 percent for all doses. The potential for serious effects is not well specified in these trials. All studies reported diarrhea and nausea and vomiting.

Summary of Non-cholinergic Neurotransmitter/Neuropeptide Modifying Agents

Haloperidol. Five studies[65-69] evaluated the effect of haloperidol relative to placebo in a total of 622 subjects with mild to moderate disease that included AD patients and mixed populations (MID/VaD/ PDD). One trial had only 15 patients, and one trial[65] lasted only 3 weeks. Two studies recruited subjects from institutions; one from the community; and, two did not specify.

Mixed results were observed for improvement in global assessment. In three of the trials there was benefit in the domain of behavior/mood which reached statistical significance. Two trials evaluated caregiver burden and found no statistically significant differences but lack of sufficient power cannot be ruled out. Few studies evaluated outcomes in quality of life/ADL. Haloperidol did not affect general cognitive function in two trials and was not evaluated in the other studies.

The quality scores for reporting adverse events varied from 1 to 5 and only three of five studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 5–17 percent for placebo and 17–33 percent in the treatment group. One trial showed a dose-response effect but the study lasted only 3 weeks. Three trials tested for differences between treatment and placebo with respect to extra-pyramidal symptoms (placebo=17–32 percent, all doses=34–97 percent), and two found statistically significant differences.[65,66] One study[66] found statistically significant differences between groups for balance-related problems.

Memantine. Three trials[70-72] evaluated memantine in 1066 patients, primarily with VaD, with 10 or 20 mg doses for durations of 12 or 28 weeks. Disease severity was moderate to severe in a single study[70] and mild to moderate in the remaining two studies.[71,72] One study included patients that were

institutionalized; one study included community subjects; and the other study did not report the source of patients.

Consistent evidence of benefit in general cognitive function was demonstrated in the two studies that evaluated this domain. Findings for global assessment are mixed. The only trial that evaluated mixed dementia populations (including some VaD) with moderate to severe dementia found statistically significant improvements in global function, behavior/mood, and quality of life/ADL outcomes, but did not evaluate general cognitive function. It should be noted that this trial with mixed populations used half the dose of memantine for half the study duration in patients with greater disease severity, and had approximately half the sample size of the other two trials evaluated in this systematic review. Despite a lower dose, a smaller number of more severely affected patients and a shorter duration, a statistically significant difference was found.

The quality scores for reporting adverse events varied from 3 to 4. Only two of three studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 3–7 percent for placebo and 9–12 percent in the treatment group. A single trial tested for differences between treatment and placebo, and none of the comparisons were significantly different statistically.

Selegiline. Six trials[73-78] evaluated selegiline in 733 patients with AD, PDD, and dementia Alzheimer's type (DA) with 10 mg per day and study duration of 60 days or 2 years.

All but one trial that evaluated general cognition showed no statistically significant changes. A single trial found statistical improvements in specific cognitive tests (Sternberg Memory tests); this trial also showed statistically significant improvements in global assessment and behavior/mood. Only this trial, which had the highest quality score (7), showed consistently positive findings across all domains tested. Three of the five trials that evaluated part or all of these domains had very small sample sizes and were likely underpowered, possibly accounting for the inconsistent findings. Based on a single trial there is evidence that selegiline and selegiline combined with vitamin E, delays the time to important functional decline milestones.

The quality scores for reporting adverse events varied from 0 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0–4 percent for placebo and 0–9 percent in the treatment group. Only one trial tested for differences between the treatment and placebo groups and showed that balance and falls were statistically significantly different (worse) between groups (particularly the group with selegiline combined with vitamin E [22 percent] versus placebo [5 percent]). However, when adjusted for multiple comparisons, these were no longer statistically significant.

Summary of Other Pharmacological Agents

Cerebrolysin. Six studies[79-84] evaluated the effect of cerebrolysin in a total of 819 subjects All but one of the trials included only AD patients with mild to moderate disease. All of the studies used the same dose of cerebrolysin, 30 ml per day for 5 days per week for 4 to 24 weeks duration. Location of recruitment was not specified.

Cerebrolysin showed a statistically significant improvement in cognition in four of five studies that evaluated this domain. Although a pooled estimate for the ADAS-cog was calculated, the model was positive for heterogeneity and the overall estimate was not statistically significant. The results for specific cognitive tests for the three trials that evaluated this domain were inconsistent. Global assessment measures showed a statistically significant effect in five of the trials. A summary estimate for the Clinical Global Impression (CGI) was presented; this model was also positive for heterogeneity but statistically significant for an overall effect. Two out of three studies showed an effect for behavior/ mood, but none of the six studies showed an effect on quality of life/ADL. No study measured caregiver burden.

Two of the six trials scored 5 out of 5 on our quality scale for rating adverse events, but did not report any adverse events. Two studies scored 4, and the other two trials scored 3 and 2. All the studies with scores equal to 4 or less tested for statistical differences in adverse events between placebo and treatment groups. Withdrawals due to adverse events were not reported in one study, and were 1 percent in two studies and none withdrew in three studies. A statistically significant difference between treatment and control group was reported in one study for weight change, anxiety, and headache.

Estrogen. Five studies[85-89] evaluated estrogens for dementia in 247 patients with primarily mild to moderate AD from the community, with the exception of one study that included moderate to severe dementia patients who were all institutionalized. One of the studies with AD patients provided 0.10 mg per day by skin patch for 8 weeks and the others used 1.25 mg per day for 12 to 52 weeks duration. The study including severe subjects used 2.5 mg per day for 4 weeks.

Three trials evaluated general cognitive function and all showed statistically non-significant findings; two trials lacked sufficient power to show changes on the ADAS-cog. Two other trials evaluated specific cognitive function but results were mixed. Most of the outcomes evaluated in the domains of global assessment, behavior/mood, and quality of life/ADL

were secondary outcomes and none showed statistically significant differences (but lack of power could be a factor).

One of the five trials scored 5 out of 5 on our quality scale for rating adverse events, but did not report any adverse event. Withdrawal rates due to adverse events ranged from 0–5 percent for placebo and 0–14 percent for the treatment group. The most frequently reported adverse event was vaginal bleeding and a single trial reported a statistically significant difference between placebo and treatment group for this symptom. It was not clear from the descriptions provided in the study if they had ascertained whether vaginal bleeding was present prior to the trial commencement.

Ginkgo biloba. Three trials[90-92] evaluated Ginkgo biloba, 120 to 240 mg per day for 3 to 12 months, in a total of 563 subjects with mixed dementias of mild to moderate severity. All were recruited from the community.

The largest trial had the longest treatment duration but the lowest daily dosage and reported a statistically significant impact for general cognitive function but had mixed findings for global assessment. A second large trial found positive changes for neuropsychological tests, global assessment, and behavior/mood outcomes with double the dosage of the previously described trial and half the treatment interval. In this RCT, clinical efficacy was assessed by using a responder analysis, with therapy response being defined as response in at least two of the three variables: CGI—global function, Syndrome Kurz test (SKT)—special cognitive function, and Nurnberger-Alters-Beobachtungs-Skala (NAB)—ADL. A single trial evaluated behavior/mood and the result was not statistically significant. No trial evaluated caregiver burden or quality of life/ADL.

All three trials scored 3 or greater on the quality scale for rating adverse events. Two studies had no withdrawals due to adverse events, and one trial had a withdrawal rate of 6 percent for both placebo and treatment groups. Two studies reported no adverse events. One study reported a statistically significant difference between the treatment and the placebo group for skin disorders. The same study reported gastrointestinal and headache adverse effects, but did not test for statistical differences between the placebo and the treatment group.

Idebenone. Four studies[93-96] evaluated the drug idebenone in 1153 subjects of mixed dementia populations of mild to moderate severity; one of these trials evaluated idebenone relative to tacrine. Doses varied from 30 mg per day to 360 mg per day, and the treatment interval ranged from 90 days to 60 weeks.

There was evidence of benefit in general cognitive function and global assessment. Several studies evaluated behavior/mood and quality of life/ADL and these outcomes were found to be statistically different. None of the trials evaluated caregiver burden.

Quality scores for reporting adverse events varied from 1 to 5. Rates of withdrawal due to adverse events varied from 0–5 percent for the placebo group and 0–5 percent in the treatment group; a single trial did not report withdrawal rates. Two trials tested for statistical differences between groups and found none. Although no clear pattern emerges, three studies identified at least one balance-related adverse event.

Oxiracetam. Five studies[97-101] evaluated oxiracetam in 554 subjects with different dementia syndromes of mild to moderate severity. All studies used 1600 mg daily, with one exception where the dose ranged between 1600-2400 mg per day. The treatment interval ranged from 90 days to 26 weeks duration.

All outcomes shown to be positive for this drug were based on Observed Cases (OC) evaluation. The two trials that evaluated general cognitive function showed benefit. The findings for specific cognitive function were mixed. A single trial evaluated global assessment and showed statistically significant change. Behavior/mood and quality of life/ADL outcomes showed mixed results. No study evaluated caregiver burden.

The quality scores for reporting adverse events varied from 2 to 5. The proportion of withdrawals due to adverse events varied from 0–9 percent for the placebo group and 0–6 percent for the treatment group. No clear pattern for adverse events is evident, but three of the five studies reported gastrointestinal related problems, primarily abdominal pain.

Pentoxifylline. Three placebo-controlled studies[102-104] evaluated pentoxifylline and one study compared pentoxifylline to sulodexide, with a total of 482 subjects with predominately MID. The dose administered in all studies was 1200 mg per day but varied between once or three times daily. The treatment intervals ranged from 12 to 36 weeks.

All three placebo trials showed statistically non-significant findings for any primary outcome evaluated on all subjects in the study. Two of these trials had very small sample sizes (n=38, n=28) and employed Observed Cases (OC) analyses; this suggests that the trials lacked sufficient power to evaluate multiple outcomes. The remaining trial had a large sample size (n=289) and employed an Intention to Treat (ITT) analysis; all primary outcomes evaluated were not statistically significant.

The quality scores for reporting adverse events were generally low, varying from 1 to 3. Withdrawal rates due to adverse events varied from 0–25 percent in the placebo group and 0–22 percent in the treatment group. The two studies that

reported adverse events indicated the presence of gastrointestinal disturbances, including abdominal pain and nausea and vomiting.

Propentofylline. Four trials[105-108] using propentofylline in 510 patients with AD and VaD were included. A dose of 900 mg per day was consistent across all studies, and the treatment duration ranged from 3 to 12 months.

Two studies with small sample sizes (n=30) showed no statistically significant results for any outcome evaluated but likely lacked power. There were two trials that found benefit in general cognitive function based on the Mini-Mental Status Exam (MMSE). The results for specific cognitive function as measured by the Digit Symbol Substitution Test (DSST) were mixed, as were those for global assessment. Behavior/mood outcomes were evaluated in a single trial and showed no statistically significant difference; this same trial evaluated quality of life/ADL and showed no statistically significant difference. No trial evaluated caregiver burden.

The quality scores for reporting adverse events varied from 1 to 4. The percentage of withdrawals varied from 0–13 percent for the placebo group and 0–12 percent for the treatment group. None of the trials tested for differences between groups. Three of the trials reported gastrointestinal events that included abdominal pain, constipation, and nausea and vomiting.

Question 2: Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?

Delay of Onset of Dementia

The concept of "delay onset" was operationalized to imply conversion from a state of cognitive impairment, classified as MCI, CLoND or CIND, to a true dementia state. No studies with this population met the final eligibility criteria, although four trials[109-112] advanced to the full text screening stage. The lack of studies eligible for evaluation in this systematic review points to a gap in the literature for pharmacological interventions (attempting to demonstrate a delay in disease onset) in MCI-type populations.

Delay of Progression of Dementia

The need for good evaluation of disease progression in trials was also identified. In general, few studies evaluated subjects in more severe states of the disease. This suggests that a bias exists towards evaluating mild to moderate disease in the trials eligible in this systematic review; this may reflect an underlying assumption that the less severe groups are most likely to benefit from drug trials. Since so few studies have evaluated the more severe groups, this assumption may require some empirical justification in future research. A consensus is required regarding the diagnostic criteria to be used to establish levels of severity.

Three studies evaluating cerebrolysin, selegiline and vitamin E, and donepezil have shown statistically significant effects in delaying disease progress in mild to moderate and moderately severe disease in patients with AD. This delay in progress was expressed in terms of delay in days to primary event or statistical differences between placebo at a specified time interval. Although these trials coincidentally evaluated dementia patients over the longest time interval, their protocol did not withdraw the drug at the end of the study. Theoretically, conclusive evidence of disease delay would be demonstrated if the treatment groups did not return to the level of the placebo. Thus, distinguishing between symptomatic and disease modifying effects is not possible unless the drug is withdrawn and the treatment groups are observed for these changes.

When studies attempted to evaluate disease progression, long-term (1 year or greater) trials continued in an "open-label fashion," where blinding was no longer maintained. This limits the confidence that bias did not affect the subsequent changes in the outcomes. It was observed that increasing levels of dropout (for a variety of reasons) also plagued these open-label phases of evaluation. From a practical perspective, maintaining adherence in longer-term trials in dementia patients is challenging, particularly for those in the placebo arm or for those with interventions that have a high proportion of adverse events. Although this practical challenge exists, the findings of this review suggest that there is a gap in the literature showing delay of the disease process of dementia related disorders.

Question 3: Are certain drugs, including alternative medicines (non-pharmaceutical) more effective than others?

Head to head comparisons of drugs in the treatment of dementia

A total of 26 [18,39,47,60,61,65,66,68,69,73,113-128] studies compared efficacy of the two or more pharmacological agents relative to each other. In general, few drugs showed statistically significant differences relative to each other. Those that did include (listed in declining order of performance):

1. Sulphomucopolysaccharides versus CDP-choline:[117] Statistically significant differences were seen in favor of sulphomucopolysaccharides in measures of behavior and global assessment in 30 institutionalized patients with mild to moderate MID.

2. Donepezil and vitamin E:[18] Statistically significant differences were seen in favor of donepezil in general cognitive function 54 patients with mild AD.
3. Antagonic stress versus nicergoline:[39] Statistically significant differences were seen in favor of antagonic stress in cognition as well as a global assessments in 62 subjects with mild to moderate AD.
4. Antagonic stress versus meclofenate:[124] Statistically significant differences were seen in favor of antagonic stress in measures of cognition and global assessment in 63 patients with mild to moderate AD.
5. Posatirelin versus citicoline:[47] Statistically significant differences were seen in favor of posatirelin in general cognitive measure and mood in 222 community living patients with mild to moderate AD.
6. Pyritinol versus hydergine:[125] A significant difference in favor of pyritinol in a global assessment measure in 102 Hispanic patients with mild to moderate AD.
7. Idebenone[61] versus tacrine: Mixed results were observed; the Efficacy Index Score showing a statistically significant benefit over tacrine, while the global assessment showed no difference in 203 individuals with AD, 44 of whom completed the study.

Current drugs approved in the United States for the treatment of dementia

What may be most relevant to clinicians are head to head comparison of the cholinergic modifying neurotransmitter pharmacological agents, particularly those currently approved for the treatment of dementia (tacrine, rivastigmine, galantamine, donepezil) in the United States. The evidence for each of these drugs has been extensively detailed, and the relative merits and handicaps of each are outlined in the results section of the full report (Chapter 3). Relative effectiveness as demonstrated by effect sizes for the ADAS-cog and the CIBIC are also compared in Chapter 3. Although, the psychometric properties of these two outcomes are commonly accepted, comparison across the populations in these pooled estimates may not lend themselves to direct comparison across these four different specific drugs; populations may be different and reporting of adverse events is not consistent. Thus, inferences about the relative efficacy of these four medications specific for the treatment of dementia should be made cautiously as head to head comparisons were not undertaken.

Question 4: Do certain patient populations benefit more from pharmacotherapy than others?

In general, very few trials examined the efficacy of dementia drugs across different populations or described the population characteristics in sufficient detail. From the 15 studies [2,3,8,10-12,23,24,61,84,93,129-132] that reported stratified analyses, eight different variables were identified, which included age, gender, Apolipoprotein E gene (APOE) genotype, disease type, disease severity (as determined by MMSE/ ADAS-cog threshold levels), treatment center, care dependence, and presence of depression. Additionally, three trials were identified that evaluated efficacy in 1) patients with Down's syndrome and dementia, 2) different races as a function of treatment center of a multicenter trial, and 3) depressed patients. Given the relatively small number of trials evaluating these variables within different populations and different pharmacological interventions, the findings of this review are inconclusive with respect to these variables. A significant gap in the literature has been identified.

Question 5: What is the evidence-base for the treatment of ischemic vascular dementia?

A total of 20 pharmacological interventions in 29 studies [17,36,38,44,46,70-72,81,92,96,98,102-104,106,107,117,126,128,133-141] were applied specifically to VaD classified dementias. The majority of these pharmacological interventions (n=14) were represented by single trials, limiting the ability to judge the evidence; these interventions included ateroid, buflomedil, cerebrolysin, sulphomucopolysaccharides (CDP choline), citalopram, donepezil, Ginkgo biloba, idebenone, minaprine, nimodipine, oxiracetam, 5-THF (trazodone), vincamine, and xantinolnicotinate. Six interventions had more than a single trial, and these included Choto-san (n=2), memantine (n=3), nicergoline (n=2), pentoxifylline (n=4), posatirelin (n=2), and propentofylline (n=2). In general, when the drug interventions were shown to be effective, it was in the domains of cognitive function (both general and specific) and global assessment. Other domains were less frequently evaluated. Several trials attempted to test for differences between VaD groups and other dementia types.

Discussion

The findings of this report suggest several important areas for future research using pharmacological treatments for dementia and these include:

Analytic framework of the intended aim of the therapy on the disease

- Better conceptualization and research design to capture "delay in progression."
- Clearer consensus on defining efficacy (benefits and clinically important change).
- Longer term studies (> 12 months).

Potential for bias

- Clarification of the role of industry sponsorship; one recommendation should be that all studies are required to disclose such information in future, including who analyzed the results.
- More concerted effort to incorporate unpublished studies and negative trials in future reviews.

Population

- Inclusion of the spectrum of severity in the patient populations (nothing to suggest that severe patients may not benefit from pharmacotherapy aimed at cognitive function improvement).
- The need for validation of trials and testing processes within cultures other than the traditional white population.
- Examining the efficacy of interventions in different sub-populations (age, disease severity levels, etc.).
- Better measurement and reporting of important patient characteristics (including baseline cognition scores, co-morbid conditions, the use of other medications, etc.).
- Inclusion of MCI type groups of subjects to evaluate "delay of onset" (studies in progress).

Outcomes

- Expansion of outcomes collected to include more than just cognitive function, and especially include caregiver burden and quality of life/ADL.
- Clear operational definitions for determining critical outcomes (delay to onset, delay to progression, important effect size, etc.).
- Understanding of how therapies are addressed and what outcomes are produced in different cultures.
- Production of other testing tools to detect both onset and responses to therapies across varied cultural groups.
- Improvement in the reporting of adverse events to evaluate harm and risk vs. benefit.
- Improvement in detailing adverse events associated with the duration period and those occurring following this period.

Analysis

- Appropriate analytical strategies that take into account intention to treat (ITT)/ last observation carried forward (LOCF) analyses; where possible both observed case and ITT/LOCF analyses should be presented.
- Sufficient data to estimate effect size, taking into account variability in both treated and control populations on the primary measures.
- Reporting the power of the study when findings are statistically non-significant.

Intervention

- Undertake more studies with direct comparison of drugs to determine the relative efficacy of agents.
- Improved description of the titration process.
- Improved collection of adverse events undertaken in a systematic fashion with standardized instruments.

Table 1. Pharmacological interventions and the number of trials (#) evaluated in this systematic review.

Cholinergic neurotransmitter modifying agents	
Antagonic Stress (2)	Metrifonate (9)
Acetyl-L-Carnitine (6)	Nicergoline (5)
Donepezil (11)	Physostigmine (4)
Eptastigmine (2)	Posatirelin (4)
Galantamine (6)	Rivastigmine (6)
Huperzine-A (2)	Sabeluzole (1)
Linopirdine (2)	Tacrine (8)
Mexofenoxate (1)	Velnacrine (3)
Non-cholinergic neurotransmitter/neuropeptide modifying agents	
Alaproclate (1)	Memantine (3)
Alprazolam (1	Mianserin (1)
Anapsos (1)	Minaprine (1)
BMY (Nootropic) (1	Moclobemide (1)
Carbamazepine (2)	Naftidrofuryl (1)
Citalopram (2)	Olanzapine (2)
Diphenhydramine (1)	Oxazepam (1)
Divalproex (2)	Paroxetine (1)
Fluoxetine (2)	Perphenazine (1)
Fluvoxamine (1)	Phosphatidylserine (2)
Haloperidol (8)	Risperidone (2)
Imipramine (1)	Selegiline (6)
Lisuride (1)	Sertraline (2)
Lorazepam (2)	Thioridazine (1)
Loxapine (2)	Tiapride (2)
Lu25-109 (1)	Trazodone (2)
Maprotiline (1)	Xanomeline (1)
Melperone (1)	
Other agents	
5'-MTHF (1)	Misoprostol (1)
Aniracetam (1)	Monosialotetrahexosylganglioside (GM-1) (1)
Amitriptyline (1)	N-Acetylcysteine (1)
Ateroid (1)	Nimesulide (1)
Buflomedil (1)	Nimodipine (2)
Cerebrolysin (6)	Nizatidine (1)
Choro-San (1)	Nootropic (1)
Choto-San (1)	ORG 2766 (2)
Citicoline (2)	Oxiracetam (5)
Cyclandelate (2)	Pentoxifylline (4)
Denbufylline (1)	Piracetam (1)
Desferrioxamine (1)	Prednisone (1)
Diclofenac (1)	Propentofylline (4)
Ergokryptine (CMB 36-733) (1)	Pyritinol (1)
Ergokryptine (Dek) (1)	Silymarin + Tacrine (1)
Estrogens (5)	Simvastatin (1)
Ginkgo Biloba (3)	Sulphomucopolysaccharides (1)
Glycosaminoglycan Polysulfate (1)	Sulodexide (1)
Guanfacine (1)	Thiamine (1)
Hydergine (1)	Vasopressin (DDAVP) (1)
Hydroxychloroquine (1)	Vincamine (1)
Idebenone (5)	Vitamin E (2)
Indomethacin (1)	Xantinolnicotinate (1)

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by McMaster University Evidence-based Practice Center under Contract No. 290-02-0020. It is expected to be available in April 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 97, *Pharmacological Treatment of Dementia*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Pharmacological Treatment of Dementia

Evidence Report

Chapter 1. Introduction

This review focuses on the pharmacological treatment of dementia. Dementia is a syndrome of acquired cognitive defects sufficient to interfere with social or occupational functioning, which results from various central neurodegenerative and ischemic processes. Dementia has become a major public health problem due to its increasing prevalence, long duration, caregiver burden, and high financial cost of care. The prevalence of dementia varies as a function of the defining criteria as shown by Erkinjuntti et al. (1997),[1] who showed a range from 3.1% using the International Classification of Diseases, Tenth Revision (ICD-10) criteria, up to 29.1% using the Diagnostic and Statistical Manual, Third Edition (DSM-III) criteria. Jorm et al. (1987)[2] conducted a meta-analysis based on 22 international studies and found that the actual prevalence rates differed significantly from study to study. However, this meta-analysis demonstrated that the prevalence increased exponentially with age. The prevalence ranged from 0.7% for 60 – 64 year olds to 24% for people over the age of 85 years. In the United States, the prevalence of Alzheimer's disease (AD) is projected to quadruple to one in 45 Americans in the next 50 years[3] across all ages. The Canadian Study of Health & Aging (CSHA)[4] estimated the prevalence of dementia in Canada at 8% (approximately 252,600 cases) in 1991 among seniors over the age of 65 years. The prevalence of dementia increases to 34% among those aged 85 years or more.[4] The age-standardized incidence of dementia in Canada has been estimated at 21.8 per thousand for females and 19.1 per thousand for males.[5] The prevalence is expected to double to half a million cases in Canada by 2013.[6] Because the world's population is progressively aging, especially in the developed nations, more people are falling into age groups where the prevalence of dementia is highest. From a clinical perspective, dementia predominately affects 1) cognition, 2) behavior/mood, 3) physical functions and activities of daily living, and 4) caregiver burden. Therapeutic interventions for dementia aim to affect these four primary domains.

Pharmacotherapy is often the primary intervention used to improve symptoms or delay the progression of dementia syndromes. The pharmacological agents used vary significantly with respect to their therapeutic actions. The most common pharmacological agents used in North America modify the activity of cholinesterases—enzymes, which degrade acetylcholine, a neurotransmitter that is critical to the neurons involved in cognition (e.g. memory, thought, and judgment). Other approaches include the use of anti-oxidants, which work by minimizing the effects of free radicals that are released through normal oxidative metabolism. These free radicals may cause neuronal damage and play a role in the development of dementia. Similarly, it is believed that inflammation contributes to nerve cell damage and dementia; hence anti-inflammatory drugs may act by decreasing inflammation, potentially reducing nerve degeneration, which may in turn slow or even prevent dementia illnesses.

Other pharmacological interventions that have been studied include cholesterol-lowering agents, anti-hypertensives, folic acid, hormones (e.g. estrogen), behavior and mood altering drugs, anti-amyloid strategies (e.g. immunization, aggregation inhibitors, and secretase inhibitors), transition metal chelators, nerve growth factors, and agents that target neurotransmitters other than acetylcholine and its receptors. The various pharmacotherapeutic agents available to treat problems associated with dementia have varying levels of evidence to support their efficacy. This report is a systematic evaluation of the evidence for pharmacological

interventions in the treatment of dementia in the domains of cognition, global function, behavior/mood, quality of life/ADL, and caregiver burden.

Diagnosis of Dementia

Determination of disease onset presents considerable difficulty, as dementia, by definition, has an insidious and gradual progression. A number of diagnostic models have been used to classify dementia. In 1988 the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) research on diagnostic criteria were published for AD, which served to increase the validity and reliability of the clinical diagnosis.[7,8] Trials published prior to this time may reflect mixed populations other than AD. Other models used to diagnose dementia include: the International Classification of Diseases (ICD) version 9 or 10, the Diagnostic and Statistical Manual of Mental Disorders (DSM) III, III-R, and IV (American Psychiatric Association), and the NINCDS/ADRDA.[9] The difficulty with these different diagnostic criteria for dementia is that they are not interchangeable. Erkinjuntti et al. (1997)[1] compared six commonly used classification schemes (DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10, and the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX)). They showed that the prevalence of dementia can differ by a factor of 10 depending on the diagnostic criteria used. Two other studies have demonstrated that the prevalence of vascular dementia (VaD) varies with the classification system and therefore these criteria for diagnosis are not interchangeable.[10,11] Furthermore, there is controversy about the validity of the clinical classification of VaD, as autopsy confirmation often does not substantiate the clinical diagnosis.[12,13] The majority of dementias were actually AD with co-existing vascular and Parkinson's disease lesions.[14] In contrast, the clinical accuracy of AD diagnosis is relatively high.[7] The discovery that a long pre-clinical period precedes AD has led to the establishment of early diagnostic indices of dementia. This border zone between normality and dementia has been given numerous names and definitions, which include: benign senescent forgetfulness (BSF), age associated memory impairment (AAMI), age-consistent memory impairment (ACMI), age-associated cognitive decline (AACD), mild cognitive impairment (MCI), cognitive loss no dementia (CLOND), and cognitive impairment but not dementia (CIND). The prevalence for this pre-clinical or mild form of cognitive decline varies with the classification system used.[15] Unfortunately, the classifications used to diagnose early mild cognitive decline are not interchangeable. MCI[16] is emerging as the preferred term for this condition[17] using the criteria of Petersen et al.[16] Ritchie et al.[18] (2001) estimated the prevalence of MCI to be 3.2% with an 11.1% conversion rate to dementia within a 3 year period.

Analytic Framework: Understanding Therapeutic Aims of Pharmacological Treatment

Dementia is a chronic progressive disease for which no known cure exists. Pharmacological interventions used to treat dementia are intended to achieve at least one of the following broad therapeutic aims:

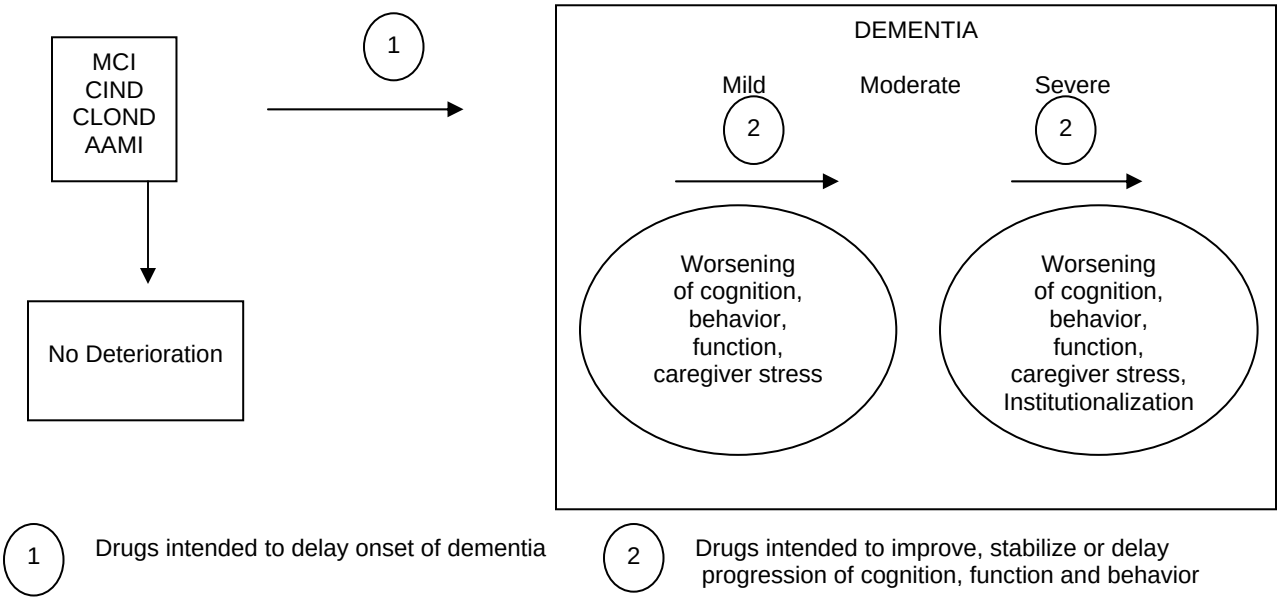
Prevention of onset of the disease. In the context of this review, this applies to those at greatest risk (such as those with the clinical diagnosis of MCI) of conversion to a dementia syndrome.

Symptomatic treatment of the disease. Symptomatic benefit can be described as maintenance (or stabilization) or improvement of the current cognitive, behavioral, functional, or caregiver status only while on active treatment with the pharmacological intervention. Withdrawal of the pharmacological therapy results in a decline towards baseline or placebo levels of relevant outcomes.

Delay in the progression of the disease. A therapeutic intervention that brings about delay in the progression of the disease can be described as either 1) one that maintains (or stabilizes) or improves current cognitive, behavioral, functional, or caregiver status, which is sustained, or 2) one that can be shown to alter the rate of decline of the disease progression, even when the drug is withdrawn.

Figure 1 details the analytic framework for the progression of dementia and shows when various pharmacological interventions would ideally be administered for the intended therapeutic benefit within this pathway. The scope of this review did not include the evaluation of normal healthy aging populations. Rather, pharmacological agents intended for populations at increased risk of conversion to dementia syndromes, such as MCI, were eligible for evaluation in this systematic review.

Figure 1. Pathway for the progression of dementia and the ideal application of drug interventions within this framework.



Understanding Efficacy of Pharmacological Interventions in Dementia Trials

It has been suggested that dementia does not have uniformly accepted criteria for disease progression or consensus regarding the magnitude of clinically important changes.[19,20] With respect to the therapeutic aim, the practical consequences of these unresolved issues are that the same efficacy variables have been used to both show evidence of symptomatic benefit and demonstrate the effects on disease progression. Thus, the design of a clinical trial (rather than the outcome) is critical to demonstrating which of these two therapeutic outcomes (symptomatic benefit or delay in progression) is being achieved with the pharmacological agent.[21]

Irrespective of which therapeutic aim is being achieved by the pharmacological agent, the lack of consensus on these two issues has even more important implications when considering the definition of "efficacy" for either treatment goal. A change in a relevant outcome measure that is due to factors other than chance is deemed statistically significant. The criteria to determine efficacy solely on statistical significance have long been recognized as problematic from an interpretation perspective. Clinically meaningful change reflects a different level of "significance" and often requires consensus among experts within the field to establish what magnitude of change is important.[20]

Efficacy as Measured by Clinical versus Statistical Significance

The dementia literature is not consistent in the criteria used for establishing efficacy, and there is no consensus on the meaning of clinical significance in the changes observed.[20,22] In general, attempts are made to select an outcome measuring an important dementia attribute (such as cognition) and an additional outcome evaluating global change as observed by a clinician (with or without input from the caregiver). The outcomes selected to reflect these two domains vary, as do the number of attributes that are selected for evaluation.

The United States Food and Drug Administration (FDA) has established criteria for efficacy of dementia (specifically AD) drug interventions,[23] which require the following: 1) a double blind, placebo-controlled trial, 2) subjects who meet established criteria for AD, 3) sufficient length of follow-up to appreciate a meaningful effect of the drug on cognition, and 4) a clinical change of sufficient magnitude to be recognized by a clinician. In establishing these criteria, it was assumed that the outcome measuring cognition was the primary change of interest, and that the global clinical evaluation would mirror the changes in the primary variable.[24] In 1997, the European Medicine Evaluation Agency (EMEA) issued new guidelines that incorporated two new concepts for the treatment of AD.[25] Firstly, the EMEA guidelines suggested a preference for a measure of functional abilities in addition to a global measure, and noted that behavioral outcomes were important from a clinical perspective. Secondly, a definition of "responders" should be included in all trials, such that the degree of improvement in their cognition (or stabilization) was pre-specified. However, the magnitude of the change reflecting a clinically meaningful change was not specifically stated in either of these two guidelines. Sufficient magnitude of the change would reflect a clinically important difference, and this would vary with the type of outcome selected.

Several authors have attempted to define "clinically" relevant change. Gutzmann et al. (2002)[26] developed an Efficacy Index Score (EIS), which is a checklist that combines dropout as well as the relevant improvements individually across the three levels of assessment (cognitive function, activities of daily living and global function). Although, this summary score has not been validated relative to other traditional outcomes, it does present a unique example of determining efficacy in the context of anti-dementia drug interventions. Mayeux and Sano (1999)[27] in reviewing drug interventions for dementia, evaluated efficacy as a percent of the change in the treatment group relative to baseline (corrected for any change in the placebo group) and contrasted this with the percent of dropouts related to adverse events. Disease progression was considered with respect to the outcomes of 1) time until death, 2) nursing home placement, 3) loss of ability to perform Activities of Daily Living (ADL), or 4) severe dementia. In the context of clinical trials seeking to establish efficacy of pharmacological interventions, the latter outcomes may be problematic to ascertain.

Evaluation of the natural history of AD established some threshold values for expected decline or progression of the disease. Using the Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-cog),[28] Rosen demonstrated that a decline of 1.28 points occurred within 12 weeks, a decline of 3.5 points within 6 months, and Stern et al. (1994)[29] showed a decline of 9 – 11 points by 1 year. Clinical experience would also suggest that the decline is not linear, with less deterioration in the early and later stages and the greatest acceleration in the middle severity category. The characteristics of the natural history of AD and other dementia types are best derived from longitudinal studies. Although, more details on the natural history of dementia are being reported, the fundamental difficulty still remains concerning the diversity of the outcome measures used to describe these changes. The picture of cognitive, behavioral, and functional decline will therefore vary with the outcome measure selected to describe it. Additionally, the diversity has a negative impact on comparisons of drug efficacy that can be made across trials.[30]

Efficacy and Outcome Measures Used in Pharmacological Intervention Trials

No specific set of commonly accepted outcomes that define efficacy or "clinical relevance" applies to all the pharmacological interventions that have been used to treat dementia. More than 175 outcome measures are listed in Appendix E. EMEA guidelines acknowledge that no single test encompasses the broad range of disease characteristics associated with AD; nor has there been convincing evidence that an ideal (or reference) instrument exists to capture cognitive, behavioral, functional, or caregiver status.[25] The FDA has recommended that "dual efficacy" of dementia drug interventions be established by significant change in both a psychological measure and a global change measure. The outcomes used to measure these attributes within these two domains were not specified. In practice, there has been a general trend in North America toward using the outcomes ADAS-cog, the Mini-Mental State Examination (MMSE), and the Clinicians' Interview-Based Impression of Change-Plus (CIBIC+) to capture the two domains when evaluating drugs for AD populations. However, these frequently used outcome measures may not be the best choice with respect to capturing "clinically relevant change". The psychometric instrument properties must also be taken into consideration. For example, it has

been suggested that the ADAS-cog is weighted predominately to evaluate memory loss at the expense of other cognitive domains (especially executive control functions),[31] which suggests that the face validity of this instrument may be in question. The generalizability of these results may be limited to dementia in which memory impairment is a key feature as the instrument is less sensitive to personality and executive dysfunction changes seen in a less typical dementia, such as frontotemporal dementia. The responsiveness (ability to detect change) of the CIBIC+ has not been well established.[32] This suggests that some of the most established outcomes used to evaluate efficacy of pharmacological interventions are far from ideal.

Demers et al. (2000)[33] critically appraised some of the most commonly used scales evaluating global assessment,[32] quality of life/ADL,[30] and behavior/mood[34] with respect to the quality of their psychometric properties. Several important limitations were identified in these reviews for the measures they evaluated, and these include 1) a lack of responsiveness data, 2) diversity in the content of the scales (capturing various aspects of a domain, for example, behavior), and 3) limited studies on reliability and validity (which are sample specific). The literature evaluating outcome measures used in dementia trials would suggest that most instruments have significant limitations, or at least more data are required to establish the required properties for acceptability of the scales.

Given the current state of development of research on outcome measures used in dementia trials for determining efficacy, a dilemma is clearly at hand. Ideally, all outcomes used to evaluate efficacy should have demonstrated acceptable psychometric properties, such as reliability, validity (construct), and responsiveness. However, since none of these outcomes have been accepted as standards, the selection of the most appropriate outcome is purely arbitrary. Similarly, establishing a rationale to exclude studies based on the specific type of outcome measure would be arbitrary. For this reason, no exclusion criteria based on outcome measures were used as eligibility criteria for this study.

Efficacy and Potential Risk of Adverse Events

Increasing attention has been given to the potential for harm, and not just benefits, when considering the efficacy of drug interventions. Empirical evidence across diverse medical fields indicates that reporting of safety information, including milder adverse events, receives much less attention than the positive efficacy outcomes.[35] Thus, an evaluation of the benefits of anti-dementia pharmacological agents alone may present a biased view of the overall benefit of the intervention. In the context of this systematic review, the type and frequency of adverse events associated with the use of a drug intervention will be scrutinized to a greater extent than previous reviews of anti-dementia drugs.

Capturing and evaluating adverse events is problematic. Typical randomized controlled trial (RCT) dose finding studies should consist of the comparison of several doses of a drug versus placebo; efficacy is demonstrated relative to a placebo group or relative to a different dose group. Ideally, the goal of early phase trials is to estimate the minimum effective dose or the maximum safe dose (or both). However, it is misleading to assume that drugs shown to be safe and effective in trials are safe and effective in all other circumstances.[36] The nature of pre-market clinical trials makes it difficult to evaluate the benefits of drugs for the universe of potential

users, as criteria restricting entry into the trial do not necessarily reflect dementia patients in general. By their nature, some adverse events are not easily anticipated, and therefore are not screened for in some trials. The implementation of pharmaco-vigilance systems attests to the need for further capture of potential adverse events not captured in trials. Adverse events may be hard to predict or anticipate and are captured only if a trial protocol was designed to measure these events. A limited number of standardized instruments exist to capture these events reliably. Unique to individuals with cognitive decline is the potential problem of validity of the self-report instrument, even if completed by the caregiver. Furthermore, many trials may be underpowered to detect adverse events with an incidence of 1/1000.[37] Despite these limitations, quality criteria for the collection and reporting of adverse events have been identified.[35,37] An instrument to evaluate the quality of reporting adverse events has been developed and used in this report to determine the strength of the evidence for adverse events in the context of determining efficacy.

Efficacy and Intention to Treat Analysis

Determining efficacy in dementia trials evaluating pharmacological interventions may vary depending on the selection of the analysis type. In general, the types of analyses of primary data in trials fall into two main categories: 1) intention to treat analyses (ITT) or last observation carried forward (LOCF), and 2) observed case (OC) or completed trial (CT). The advantages of ITT over OC analyses have been well explicated.[38] It is recognized that non-compliance is not a random event; thus, ITT analyses should be used to base principal conclusions of efficacy.[39] In the context of some anti-dementia drug therapies, where dropout rates due to adverse events and other non-compliance reasons may be high, the ITT analysis minimizes bias and the potential for type I errors when considering treatment efficacy. However, the ITT analysis, while less biased, does tend to reduce treatment effects to the extent that there are dropouts and crossover patients. The optimal analysis, when there is a large loss to follow-up, is to conduct the analysis both ways and look for consistency.

Primary Objectives and Scope of Systematic Review

A large number of pharmacological interventions have been studied in dementia patients. These agents can be classified into three broad categories: 1) cholinergic neurotransmitter modifying agents, such as acetylcholinesterase inhibitors, 2) non-cholinergic neurotransmitter/ neuropeptide modifying agents, and 3) other pharmacological agents. Although only four agents have been approved by the FDA for the treatment of dementia, many other pharmacological agents are being evaluated in trials in off-label use. In both these circumstances, there was a need to determine the evidence to support claims of efficacy and to describe adverse events.

The Questions

Given the range of pharmacological agents that have been used to treat dementia, evaluation of all of these interventions in a systematic review (which afforded a consistent methodology) should serve as a meaningful contribution in this area. The purpose of this systematic review is to answer the following questions:

1) *Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?*
2) *Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?*
3) *Are certain drugs, including alternative medicines (non-pharmaceutical), more effective than others?*
4) *Do certain patient populations benefit more from pharmacotherapy than others?*
5) *What is the evidence base for the treatment of VaD?*

This review considers different dementia populations (not just AD) and subjects from both community and institutional settings. The interventions were limited to pharmacological agents (including nutriceuticals), and these were not restricted to those that have received official approval in North America. The studies eligible in this systematic review were restricted to parallel RCTs, but the study outcomes were not limited to specific types.

The review will serve to evaluate the quality of the evidence and identify important gaps in the literature. Future recommendations will serve the dementia research community specifically. This evidence report will support the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) in developing "best practices" and practice guidelines for the evidence-based treatment of dementia for providers, patients and the public.

Chapter 2. Methods

The Research Team

A multidisciplinary local research team representing geriatric and dementia epidemiology/ systematic review methods (P. Raina, PhD), pharmaco-epidemiology (M. Levine, MD, PhD), geriatric medicine/ dementia (D. Cowan, MD; C. Patterson, MD), rehabilitation/ systematic review methods (P. Santaguida, PT, PhD), and neuropsychology (A. Unsal, PhD) was assembled. The core research team, including experienced staff at the McMaster Evidence-based Practice Center (EPC) (F. Baldassarre, MSc; L. Booker, BA; M. Gauld, BA) participated in regular meetings and reached consensus on key methodological issues. An international Technical Expert Panel (TEP) was assembled to provide high-level content expertise in dementia and participated in conference calls on an as-needed basis. Participants in this panel were: Larry W. Chambers, PhD. Ottawa, ON, Canada; Thomas Cook, MD. (ACP appointee) Colorado Springs, CO, USA; Rachelle Doody, MD, PhD. Houston, TX, USA; John Feightner, MSc, MD. London, ON, Canada; Rodney Hornbake, MD. (ACP appointee) Hadlyme, CT, USA; David Hogan, MD. Calgary, AB, Canada; Roy Jones, MD. Bath, UK; and Holly Tuokko, PhD. Victoria, BC, Canada.

Topic Assessment and Refinement

Refinement of Questions

The first step during the topic assessment and refinement process was to organize a teleconference with the partner organization, the Task Order Officer (TOO), invited topic experts, and the McMaster team in order to define the magnitude of the topic addressed and to refine/clarify the preliminary research questions for this evidence report. It was agreed that this evidence report would focus on addressing the efficacy of pharmacotherapies for dementia syndromes. Regular teleconferences were held with the TOO, the partner, and technical experts throughout the data refinement and extraction phase.

Search Strategy

Search strategies were developed and undertaken in the electronic databases listed in Table 1 for the time periods specified. The order of the databases in Table 1 also represents the sequence that the databases were searched. Appendix A details the search terms for all databases.

Table 1. Databases searched for relevant RCTs.

Database searched	Search date	Period searched
Cochrane Central	February 3, 2003	1st Quarter 2003
MEDLINE® & PreMedline®	February 4, 2003	1998 to 2003 week 4
EMBASE	February 6, 2003	1998 to 2003 week 5
AMED	March 4, 2003	1985 to 2003 February
CINAHL®	March 5, 2003	1982 to February 2003 week 3
Ageline	March 6, 2003	1978 to 2002 December
PsycINFO	March 7, 2003	1967 to 2002 December

Expert opinion was sought on the most efficient search strategies to minimize noise in the collection of citations. Some of the medical subject headings (MeSH) used to select RCTs yielded a large number of non-RCT literature due to misclassification of the study design terms. For example, in previous indexing, terms like "longitudinal study" or "comparative study" were applied to RCTs; conversely, the MeSH terms "random" or "randomized" in the title or abstract were not consistently used. However, some recent methodological work has suggested that more specific search term approaches can be used, which increases the sensitivity and specificity of the search results.[40] The Cochrane Central Trial Registry contains correctly re-classified RCT/Controlled Clinical Trial (CCT) trials that were misclassified in MEDLINE® and EMBASE from 1966 to 1998. All published RCTs to 1998 are contained within this database. Hence we commenced our search with the Cochrane Central Trial Registry database. For this reason, MEDLINE® and EMBASE were searched from 1998 forward for relevant studies, and all the other databases from their inception.

Specific drug names and manufacturer brands were considered as potential search terms. However, the local research team was in agreement that listing specific drug names would bias the yield to include only those pharmacological agents searched and would not capture newer drug therapies. Thus the recommendation was to not restrict the search to known pharmacological agents but to include whatever agents were in the literature.

In addition to the electronic databases, the bibliographies of retrieved papers were retrieved. Any citations recommended by the local research team, the TEP, or the peer reviewers were retrieved and screened.

Eligibility Criteria

Inclusion. Studies were included that contained the following criteria:

1) Age: Studies involving dementia patients who were 18 years or older in age
2) Diagnostic model used to determine dementia: The diagnosis of dementia using any of these criteria:
   i) ICD 9 or 10.[41,42]
   ii) DSM III, III-R, and IV.[43,44,45]
   iii) NINCDS.[9]
   iv) NINCDS-ADRDA[9] or NINCDS-AIREN.[46]

3) Diagnostic criteria used to determine cognitive impairment (pre-dementia): In the case of not yet diagnosed dementia, specific diagnostic categories were accepted for the following:
   i) mild cognitive impairment (MCI)..[47]
   ii) cognitive impairment not dementia (CIND).[48]
   iii) cognitive loss no dementia (CLoND).[49]
4) Disease classifications for dementia: These included AD, senile dementia of the Alzheimer's type (SDAT), Lewy body disease, VaD, multi-infarct dementia (MID), AIDS/HIV dementia, Parkinson's disease dementia (PDD), progressive supranuclear palsy (PSP), mixed diagnosis dementia, encephalopathy, Mesulam syndrome, progressive non-fluent aphasia, Binswanger disease, subcortical leukoencephalopathy, circumscribed lobar brain atrophy, Pick disease, amyloid beta-protein (not Down's syndrome or trisomy), cerebral amyloid angiopathy, neurofibrillary tangles, threads, senile plaques, corticobasil ganglionic degeneration, cerebral autosomal dominant ischemia with subcortical leukoencephalopathy (CADISIL), Huntington's disease with dementia, hydrocephalus (for additional terms used in the search strategy, see Appendix A).
5) Severity classification: This was accepted in whichever classification system the studies specified. The majority of studies specified threshold criteria using the MMSE as follows: mild > 22, moderate 14 – 21, and 10 – 14 as severe. Many studies used the definition of mild to moderate as a range from 10 to 26 based on criteria established by Folstein et al.[50] Some studies specified a category (i.e. mild to moderate) but did not report the baseline MMSE values for the groups compared.

Some studies specified two categories (mild to moderate) and (moderate to severe) based on the DSM-III-R criteria. Cambridge Examination for Mental Disorders in the Elderly (CAMDEX) specifies levels of severity (minimal, mild, moderate, severe). Similarly, some studies reported a category of severity without stating which method was used. In these instances, the category of severity specified was accepted as reported by the study authors.

Exclusion. Studies that had populations with any of the characteristics listed below were excluded.

1) Dementia disease classification: i) alcohol caused dementia/ Korsakoff's syndrome, ii) Creutzfeldt-Jakob syndrome, c) spongiform encephalopathy, iii) hypothyroidism, iv) vitamin B12 deficiency, v) neurosyphilis.
2) Dementia diagnosed using only Lowb, Hachinski (specific for VaD) criteria.[51]
3) All organically caused dementias which includes "Delirium, Dementia, Amnesic Disorders, and Cognitive Disorder Otherwise Specified. The predominant disturbance is a clinically significant deficit in cognition that represents a significant change from a previous level of functioning. For each disorder in this section, the etiology is either a general medical condition (although the specific general medical condition may not be identifiable) or a substance (i.e., a drug of abuse, medication, or toxin), or a combination of these factors."[43]
4) Temporary dementia (e.g. side effect of anesthesia) classified as follows: Delirium: a delirium is characterized by a disturbance of consciousness and a change in cognition

that develop over a short period of time. The disorders included in the "Delirium" section are listed according to presumed etiology: delirium due to a general medical condition, substance-induced delirium (i.e. due to a drug of abuse, a medication, or toxin exposure), delirium due to multiple etiologies, or delirium not otherwise specified (if the etiology is indeterminate).

5) Normal or healthy volunteers: studies that deal with healthy people (i.e. prevention is limited to people who have any form of the above); volunteer study population
6) General population of elderly persons.
7) Study subjects selected for depression (some patients may have dementia but not all) and where there is no stratified analysis by disease subgroup (i.e. the dementia subjects).

Study Design. Eligible studies included parallel design RCTs only. Although crossover trials are suitable for chronic diseases, they may be prone to period effects or period by treatment interactions. Period effects are systematic changes in the outcome that apply to all patients due to temporal changes in the disease or to the measurement instrument. Period by treatment interactions occur when the efficacy of the intervention varies by period. Additionally, a carry-over effect may occur if there is not an adequate washout period. Apart from the weaknesses of this design, some limitations arise when considering the potential for meta-analytic analyses. Traditionally, first period data from a crossover trial are abstracted and can be potentially combined with parallel trials for analyses of a pooled estimate; the reporting of the study results (positive or negative) would also be based on this first period data. In a preliminary phase of the review, several crossover trials were examined. Many did not report first period data, which precluded any potential for combining with parallel trials; many trials also did not undertake statistical tests during the first experience, thus making it difficult to report the direction and significance of the first period findings. Finally, because this systematic review was considering a variety of drug interventions administered over differing time intervals, period effects might be an important source of bias. For all these reasons, the decision was made to exclude crossover trials from this systematic review.

Language of Publication. Studies published in the English language were eligible. The scope and resources of this review did not permit translation of studies published in other languages.

Sample Size. No sample size restrictions were applied.

Treatment Interventions. Drug interventions were eligible in the following manner:

1) Pharmacological agents: all types of pharmacological treatment were considered in this review, including food supplements (as defined by the FDA). Government approval was not a requirement, and as such, off-label use of drugs (i.e. drugs approved for other conditions but used in the treatment of dementia) were eligible for this review.
2) Dose: all doses and dosing schedules and any mode of administration (oral, subdermal, transdermal, intravenous, suppository, or intra-muscular injection) were considered.
3) Treatment period: the period of treatment must equal or exceed 1 day.

4) Follow-up length: Any duration of follow-up was eligible. Different drugs require different time periods to show an effect. For example, antidepressant and anti-psychotic medications may take a month or more to be effective. Some dementia drugs take a minimum of 2 months. For interventions such as vitamin E or Ginkgo biloba, the time to effect is not well established. Thus, an absolute limit to the minimum number of months of follow-up could not be applied to all potential interventions. It was anticipated that many studies with some of the most recent pharmacological agents (i.e. donepezil) would have a minimum follow-up of 24 weeks.

Study Outcomes. No specific set of commonly accepted outcomes that define efficacy or "clinical relevance" were applicable to all the pharmacological interventions that have been used to treat dementia. The literature evaluating outcome measures in dementia trials would suggest that most instruments have significant limitations or at least more data are required to establish the required properties for acceptability of the scales. Since none of the outcomes used in dementia trials have been accepted as standards (no consensus), the selection of the most appropriate or clinically relevant outcome is purely arbitrary. Similarly, establishing a rationale to exclude studies based on the specific type of outcome measure would be arbitrary. For this reason, no exclusion criteria based on outcome measures were used as eligibility criteria for this study; rather the domains of interest for inclusion have been identified.

Studies with the following outcomes were included:

- General cognitive function (e.g., ADAS-cog).
- Specific cognitive function (e.g., Weschler Memory Tests).
- Global clinical assessment (e.g., CIBIC).
- Behavior/mood (disturbances characterized by agitation, wandering, sleep cycle disturbance, depression, obsessive compulsive activities) (e.g., Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE_AD)).
- Quality of life/ADL (e.g., Instrumental Activities of Daily Living (IADL)).
- Effects on primary caregiver (also referred to as caregiver burden).
- Safety as measured by the incidence of adverse effects (e.g., particularly serious adverse events).
- Acceptability of treatment as measured by withdrawal rate from trial due to side effects of the medication. (e.g., dropouts due to adverse events).
- Mortality.
- Dependency or Rate of Institutionalization/ or continued residence in own home.
- Use of services.

Studies with the following outcomes were excluded as follows:

- Studies which reported only biological/ physiological outcomes, such as plasma levels, changes on functional imaging, or electroencephalography (EEG) activity, were noted but not assessed as efficacy measures.

- Outcomes reported in the trials should reflect changes in the person with dementia. If the study population did not all have dementia, only data subgrouped for dementia was examined.

Minimum quality threshold score for eligibility.

Exclusion part I: Pre-Jadad score. Studies were also screened to determine a minimum threshold for quality, sometimes described as "fatal flaws" in the trial design. Specifically, all studies had to include at least some mention of the term "randomization" or "withdrawal(s)" in the text of the paper. Trials that did not at least mention these components were excluded, as they possessed a fatal flaw.

Exclusion part II: Post-Jadad score. The methodological quality of the primary studies was assessed using the modified Jadad scale for RCTs[52] (Appendix B). The reliability of this modified scale was shown to be high, as measured by the intraclass correlation coefficient (ICC = 0.90).[52] Each study was evaluated by two reviewers, and the level of agreement was determined statistically. The first three items on the scale rate elements that have been shown to bias meta-analytic results. These include randomization, blinding, and withdrawal. If these items alone are considered, the maximum score is 5. Any study that did not score 3 or more on the scale was excluded from the review. Therefore, this review abstracts detailed data only from studies that achieved moderate to high ratings on the quality scale.

Evaluating the methodological quality of studies and rating the strength of the evidence.

Quality of the RCT. The methodological quality of the primary studies was assessed using the modified Jadad scale for RCTs.[52]

Quality of reporting adverse events. The potential for risk, or adverse events, was an important component to consider with respect to efficacy. The Jadad scale for quality does not take into account factors associated with adequate collection and reporting of adverse events as detailed by Ioannidis and Lau (2002).[35] Therefore, a summary checklist was developed to determine the potential quality in the collection and reporting of adverse events (Appendix B). This score was used to evaluate the relative quality of the adverse events reported.

Data Collection and Reliability of Study Selection

During the identification phase, two independent reviewers evaluated the title and abstract for eligibility; those meeting the criteria were retrieved as well as those that reported insufficient information to determine eligibility. Two independent reviewers examined the full text of these articles (passing from the title and abstract phase). All studies meeting eligibility criteria were reviewed to assess quality and abstracted according to predetermined criteria. The articles were grouped according to the pharmacological agent used in the intervention.

A team of study assistants was trained in the eligibility criteria for the purposes of this systematic review. Standardized forms and a guide explaining the criteria were developed from previous templates (Appendix B). Two reviewers were used for the identification, selection,

validity, and abstraction phases of the systematic review. Disagreements were resolved by consensus. The reviewers were experienced EPC staff with post-graduate training in research methods. The reviewers and abstractors would consult with more senior members of the TEP for content expertise or methods-related issues.

Summarizing Results: Descriptive and Analytic Approaches

It was expected that studies of the pharmacological agents used in the management of dementia would be quite diverse with respect to the intended therapeutic effect. For these studies, evidence and summary tables (Appendix C) were constructed to describe the more salient characteristics of the included studies.

Meta-analysis

Statistical meta-analysis was not appropriate for all outcomes or interventions. Before calculating a pooled effect measure, the reasonableness of pooling was assessed on clinical and biological grounds, in terms of clinical homogeneity. Tabular summaries of key characteristics, participants, interventions, and outcomes were considered. A priori, it was decided that pooled estimates would be undertaken for studies with the same pharmacological intervention and the same outcome measure and that a minimum of three studies was necessary for pooling for a specific outcome[*]. Consideration was given to the similarity of study populations when selecting studies to be included in the pooled estimates. Although many studies evaluated multiple outcomes, data necessary for meta-analysis were not provided in all eligible trials. When sufficient data were provided to estimate the weighted mean difference (WMD), then a meta-analysis was undertaken. WMD was selected as the pooled estimate (versus the standardized mean difference) because the outcome measures did not differ between studies eligible for pooled estimates. For WMD, the difference between the treated and control groups are weighted by the inverse of the variance.

Analysis was undertaken in RevMan 4.2 (Review Manager, Cochrane Collaboration, 2003), and the random-effects model was used to conduct our analyses. In cases where heterogeneity existed, the results of the random-effects model only were considered for interpretation of the results of the pooled estimate. RevMan 4.2 automatically tests the homogeneity of the results of the individual studies for each comparison of dichotomous or continuous data. Tests of homogeneity are formal statistical analyses for examining whether the observed variation in study results is compatible with the variation expected by chance alone. The more significant the results of the test (the smaller the p-value), the more likely that the observed differences were due to unknown factors likely not controlled for in the study. Sensitivity analysis or meta-regression was not undertaken to assess the extent to which the methodological quality of studies, population characteristics, dose, etc., accounted for variation in the primary outcome.

* A priori it was decided that a minimum of three studies would be required for undertaking pooled estimates. It was assumed that if two studies were meta-analyzed, theoretically the estimates could be in opposite directions leading to un-interpretable estimates. In this same situation, a third study would allow for interpretation of the direction of the effect.

Power Analyses

Power analyses were conducted for select pharmacological interventions reporting non-significant findings for all primary outcomes reported in the paper. In addition, if the trial reported the outcomes of MMSE, ADAS-cog, or the CIBIC+, the power for these was also estimated. It was assumed that the desired level of significance was set to alpha equal to 0.05. Adequate power was defined as at least 80% power.

Peer Review Process

A list of potential peer reviewers was created at the outset of the study. During the course of the project, additional names were added to this list by the McMaster Center and Agency for Healthcare Research and Quality (AHRQ). In May 2003, the individuals on the list were approached by the McMaster team and asked if they would act as peer reviewers of this evidence report. A total of 26 experts agreed and received a copy of the draft report and a copy of the "Structured Format for Referee's Comments" (Appendix D). A list of the reviewers' names and their affiliation is provided in Appendix D. In addition, a criticism editor, Dr. Patricia Huston, who is external to the McMaster EPC, was asked to review the draft report and synthesize the peer review comments. The report from the criticism editor was then used to prioritize the incorporation of peer review comments into the final version of this evidence report.

Chapter 3. Results

In this chapter, the presentations of the main results of the systematic review are organized according to the five questions that were addressed. The first question, concerning efficacy of the pharmacological interventions, contains results from all eligible studies. Subsets of trials were then selected from this larger set to address the remaining four questions (see Chapter 2 Methods).

Eligible Studies

Figure 2 shows the final yield of eligible studies for evaluation, and the inclusion/exclusion criteria are listed in Chapter 2. Approximately 10.5% of identified studies met the eligibility criteria in the title and abstract phase. Similarly, 14.7% of the full text screened citations were eligible for full data abstraction. Several trials were identified as "companion papers", indicating that results for these related studies were based on the same study subjects. These related studies were evaluated and a main publication was selected (usually the first chronological publication), and the remaining trials were searched for any additional data for abstraction; the "companion papers" were not considered as unique studies. English-language reports only were included in this review.[53] Although this is acknowledged as a possible source of bias, the overall proportion of potentially eligible non-English studies for review in title and abstract was small (7%).

Figure 3 indicates the distribution of eligible studies as a function of publication year grouped into approximately 5-year intervals. The largest proportion of studies (83%) was published within the last 11 years, with the greatest number from 1997 forward. This may have some implications for future systematic reviews with respect to the years searched.

This systematic review yielded a total of 97 pharmacological agents used in the treatment of dementia from 186 unique studies. These 97 interventions have been classified according to three broad categories: 1) cholinergic neurotransmitter modifying agents, 2) non-cholinergic neurotransmitter/ neuropeptide modifying agents, and 3) other agents.

Question 1: Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?

The largest number of eligible citations evaluated was cholinergic neurotransmitter modifying agents (n = 72). The remaining citations were distributed amongst the non-cholinergic neurotransmitter/neuropeptide modifying agents (n = 61) and other agents (n = 76) categories. Some studies evaluated agents in more than one category. The results for all pharmacological agents are presented in this chapter in summary format with descriptive text and an overall summary table (OST) for each drug located at the end of this chapter. The specific details abstracted from each individual study are presented within Appendix C (guide to the results tables) and organized into these same three therapeutic effect classification groups and by pharmacological agent. These Evidence Tables are available on-line at http://www.ahrq.gov/clinic/epcindex.htm.

Figure 2. Flow diagram showing the final number of studies meeting the eligibility criteria.

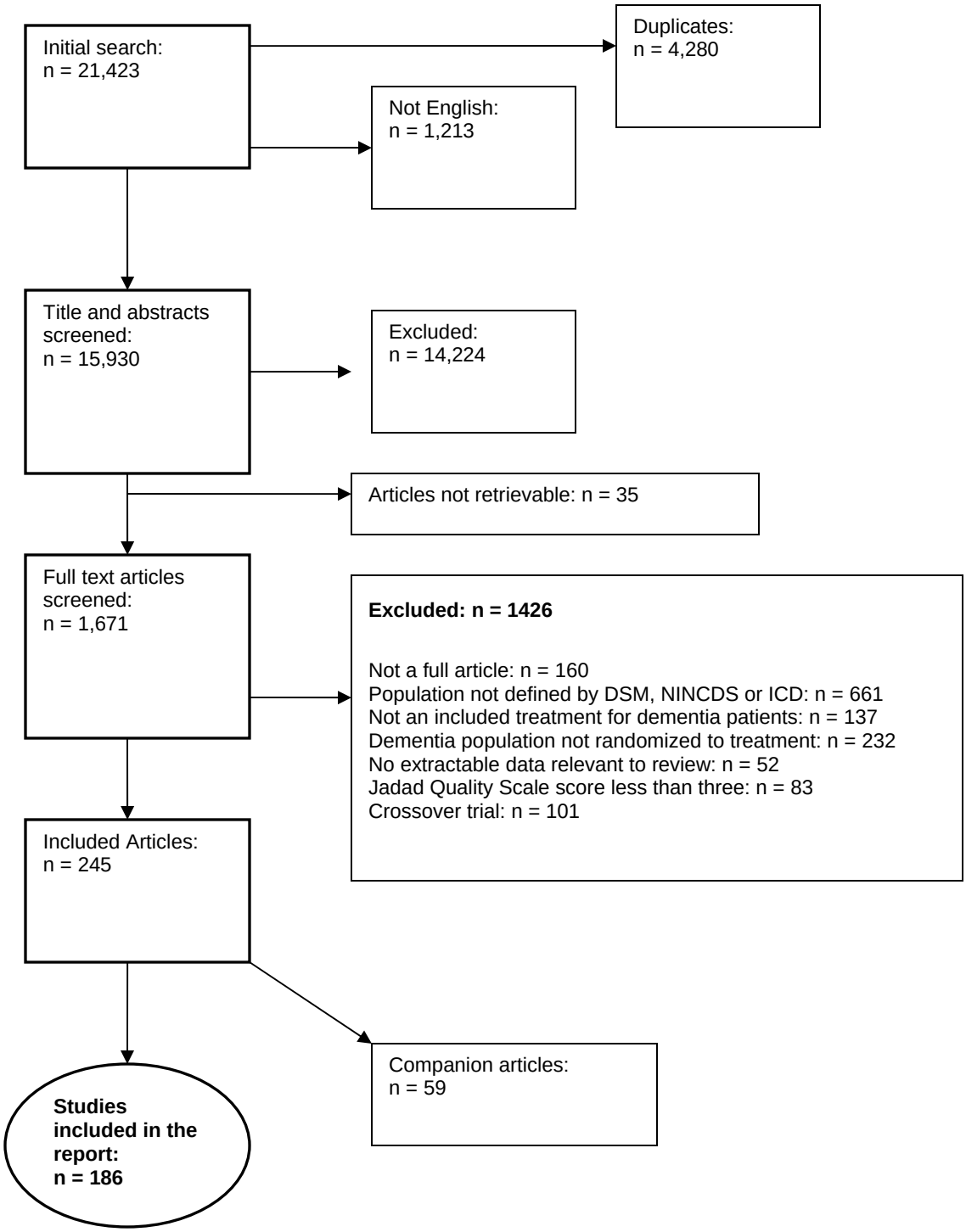
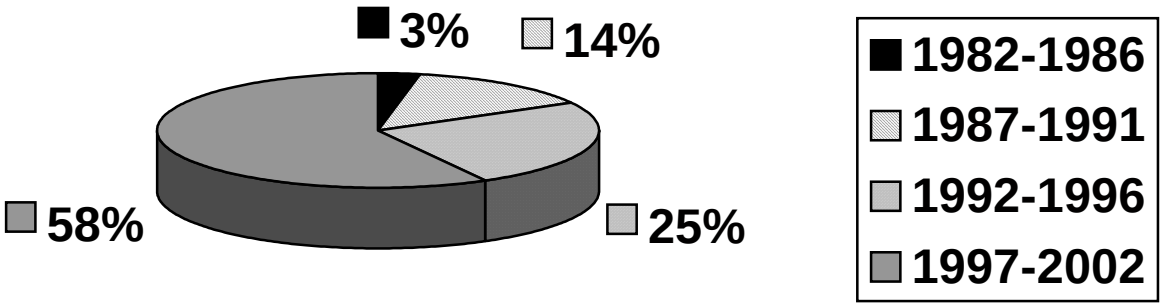


Figure 3. Proportion of studies as a function of year of publication.



Appendix C contains three sets of tables with key study descriptors as follows:

Key characteristics. Summarizes the following aspects of each study: features (author, year published, funding source, modified Jadad scale quality score, number randomized, number completing the trial, subgroup analysis), population characteristics (diagnosis, criteria for diagnosis, disease severity, percent male, age, dwelling, and differentiating demographics), intervention (doses, titration scheme, and intervention period), and a complete list of outcomes administered in the study protocol.

Study results. Details the changes observed (the magnitude of theses changes, the comparison groups analyzed, and the findings of any statistical testing) for those outcomes for which appropriate data was reported (for up to three time periods if available). When reported in studies, baseline measures, particularly MMSE score, were also detailed in these tables.

Study adverse events. Lists the specific types of adverse events (side effects, adverse reactions, and serious events) reported, any statistically significant differences between groups, the proportion of withdrawals due to adverse events, and the quality rating score (based on a checklist devised at the McMaster EPC and on the work of Ioannidis and Lau (2002)[35]) specific to the collection and reporting of these adverse events.

Interpretation of the Results in the Overall Summary Tables (OST) for Individual Studies

To facilitate the presentation of information within the OST (found at the end of this chapter), the outcomes reported in eligible studies were classified into seven domains: 1) general cognition scales, 2) specific cognition tests (neuropsychological tests evaluating specific attributes of cognition, such as short- and long-term memory, word fluency, etc.), 3) global assessment, 4) behavior/mood, 5) quality of life/ADL, 6) caregiver burden, and 7) other. The EPC research team reached consensus on the classification of the various outcome measures within these seven domains. For example, the ADAS-cog and MMSE were classified as "general cognition scales", and the BEHAVE-AD and NOSGER were placed in the "behavior and mood" domain (see Appendix C guide to the results tables). The complete list of outcomes that were reported in the studies evaluated in this review and the domains that they were classified within is found in Appendix E. Table 9 in the report presents a guide to the overall summary tables by domain.

For each of the outcomes reported by a study, four interpretations of the results were possible. The four options for interpretation are as follows:

SC = *significant change.* Demonstrated by statistical significance ($p \leq 0.05$) for the primary outcomes from an ITT analysis comparing treatment and placebo groups, or comparing differences among dose groups.

NS = *not significant.* The corollary of SC indicating no statistical significance.

MX = *mixed results.* Primary outcomes within the same domain show opposite or inconclusive statistical significance; for example, in the general cognition domain, half the studies show significant change and the other half show no significance).

NR = *not reported.* Outcome was collected but not statistically evaluated or not reported in the publication.

NT = *not tested.* No outcomes in this domain were tested.

Secondary outcome results were reported in the absence of any primary outcome data (for the domain of interest) and were demarcated with a (2^o) in the OST. Similarly, analyses other than ITT were denoted with an asterisk (*) in the OST. If the report describes my subgroup analyses, the word SUBGROUP appears in the "other" column.

Adverse events were not always clearly described in many studies. A priori, we selected 5 generic symptoms (nausea, dizziness, agitation, eating disorder, and diarrhea) and selected to detail the ranges amongst studies for both placebo and treatment groups for these symptoms. The percent of withdrawals for both groups due to adverse events was reported. Adverse events reported to be statistically significant are highlighted for the reader. The details in addition to the quality score rating will assist the reader in evaluating the potential for harm.

Statistical Analysis

Power Analyses and Measures of Effect for combined studies. Power analyses (PW) were for individual trials for select pharmacological interventions (donepezil, galantamine, tacrine, rivastigmine, memantine, estrogen, carnitine, ginkgo biloba, selegiline) for all primary outcomes. In addition, if the trial reported the outcomes of the MMSE, ADAS-cog, or CIBIC+, power was also estimated (for individual trials of pharmacological interventions that had a minimum of three trials with a common outcome). Quantitative meta-analyses were undertaken in interventions that had a minimum of three trials using the same outcome scales and which provided sufficient data to permit calculation of effect sizes (as an Odds Ratio (OR), Relative Risk (RR) and Weighted mean difference (WMD)). The random-effects model results are presented to the reader.

Quantitative and Descriptive Analyses

Results of cholinergic neurotransmitter modifying agents (CNMA)

A total of 70 studies evaluating 16 cholinergic neurotransmitter modifying agents were eligible for review (Table 2). Six studies directly compared different drugs, and these trials are considered separately in the section that addresses question three. Overall results for each of the trials for each of the interventions are detailed in the OST located at the end of this chapter and organized by drug. All other study details are available in Evidence Tables 1 through 93 in Appendix C.

Table 2. List of Cholinergic neurotransmitter modifying agents and the number of studies vs. placebo for each of these. Asterisk (*) indicates report of a drug vs. drug trial [comparator drug(s) in brackets].

Drug	Number of studies vs. placebo	Drug	Number of studies vs. placebo
Antagonic Stress * [Meclofenoxate] *[Nicergoline]	0**	Metrifonate	9
Carnitine	6	Nicergoline*[Antagonic Stress]	4*
Donepezil *[Vitamin E]	10*	Physostigmine	4
Eptastigmine	2	Posatirelin *[Citicoline]	4*
Galantamine	6	Rivastigmine	6
Huperzine-A *[Tablet Capsule]	1*	Sabeluzole	1
Linopirdine	2	Tacrine *[Idebenone] *[Silymarin]	6**
Mexofenoxate *[Antagonic stress]	0*	Velnacrine	3

Carnitine (also known as acetyl-L-carnitine, gamma-trimethyl-β-acetylbutyrobetaine (Alcar). See Evidence Tables 1 through 8 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. A total of six studies[54,55,56,57,58,59] evaluating carnitine were included in this review. Four of the reports were published from 1990 to 1992[56,57,58,59] while the remaining two, both by same authors, were published in 1996 and 2000.[55,54]

Design/methodology. A total of 925 subjects were evaluated in these six studies comparing carnitine and placebo. The range of study sample sizes was from 30 to 431 subjects. Quality scores (out of 8 points) ranged from moderate[57] (5) to high[58,59] (7), and all of the studies were partially or totally funded by industry.

Populations. All trials were conducted on AD patients, and all but one study used the NINCDS criteria for diagnosis. None of the trials reported including patients with severe dementia; all were classified as mild to moderate.

One trial[58] had a mix of community and institutional patients, and one study reported using a community sample.[56] The mean age of the samples ranged from 59[54] to 79 years,[59] with the majority reporting mean age greater than 70 years. One study[56] did not report mean age. Three studies specified the baseline MMSE[54,55,57] (range 16.1 to 20.6) and one trial specified the modified MMSE[56] (mean 35) demonstrating no differences between placebo and treatment groups.

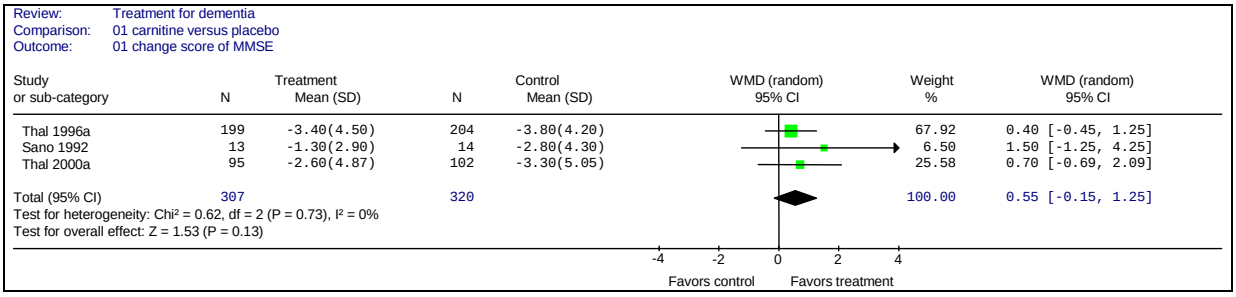
Intervention. The dose varied from 2 to 3 grams per day, and treatment duration was either 24 weeks[56,57,59] or 52 weeks.[54,55,58] One study[57] did not report the dose used. No titration period was used for this drug in any of the studies.

Primary outcomes. All of the studies measured cognition as a main outcome; half of the trials also measured outcomes in the behavior/mood domain.[58,54,55] All but one of the studies[58] used a quality of life/ADL or functional status measure. Only one study[55] evaluated caregiver burden. Of the four studies[59,58,54,55] reporting the findings from a global measure, only one[55] used the Caregiver-rated Global Impression of Change (CGIC).

Analysis. Half of the studies reported ITT analyses[58,54,55] and the remaining trials reported OC results.[57,59,56] The ability to combine results was limited with only three studies having the common outcomes of ADAS-cog, modified MMSE (mMMSE), and Clinical Dementia Rating (CDR).

Results and interpretation. See Summary Table 1. The four studies that evaluated "general cognitive function" did not find statistically significant differences in this domain. For those trials that provided sufficient data to estimate power, three trials[54,55,56] were underpowered for the MMSE (PW = 0.15 to 0.19), and two trials[54,55] for the ADAS-cog (PW = 0.08 to 0.09) and the CDR (PW = 0.06 to 0.11). Meta-analysis was undertaken for the MMSE scores; although favoring a treatment effect, the pooled effect size (WMD = 0.55) was modest and zero was contained within the confidence interval (Figure 4) for the random effects models. The pooled estimate favoring treatment may suggest some potential for benefit in general cognitive function, but this must be verified in future research.

Figure 4. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the MMSE comparing carnitine versus placebo.



For "specific cognitive tests", two out of four studies did not detect statistical differences relative to placebo, and the remaining two showed mixed results (see Summary Table 1). No significant differences were found in the domains of global assessment, behavior/mood, and quality of life/ADL; power could not be evaluated for the majority of these outcomes in the trials (insufficient data reported to permit calculation).

Four[57,59,56,58] of the six trials scored 3 out of 5 on our quality scale for rating adverse events. Two trials[55,54] did not adequately report adverse events (score = 1), but tested for statistical differences between groups. Withdrawal rates due to adverse events ranged from 0 – 3% in all studies, with the exception of a single trial[59] where the percentage was 22% (placebo) and 44% (treatment). The high rates in this trial are likely related to the small sample size (n = 36). This same trial[59] was also the sole study reporting dizziness and anxiety (confusion, depression). In general, gastrointestinal symptoms (Evidence Table 8) were the most frequently reported adverse events, but most studies did not test for statistical differences in the rates between the groups. The percent of subjects reporting of a priori selected symptoms across all studies are as follows: 1) nausea (placebo = 6 - 14%, all doses carnitine = 28%), 2) dizziness (not reported as an event for either placebo or treatment group), 3) agitation (placebo = 6%, all doses carnitine = 7%), 4) diarrhea (not reported as an event for either placebo or treatment group), and 4) eating disorder (not reported as an event for either placebo or treatment group).

Donepezil. See Evidence Tables 9 through 21 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. A total of 11 studies[60,61,62,63,64,65,66,67,68,69,70] evaluating donepezil were eligible for this systematic review. One study [70] compared donepezil to vitamin E rather than placebo. All were published within the last 6 years (n = 1, 1996), (n = 2, 1998), (n = 1, 1999), (n = 5, 2001), (n = 2, 2002). Three of these studies[66,67,69] were undertaken by the same research group at different time periods and had unrelated cohorts of patients.

Design/methodology. A total of 3239 subjects (range of study sample size, 30 – 893) were included in these trials. The modified Jadad scale quality scores ranged from 5[61] to 8.[63,64] All studies were funded by industry sponsors with the exception of a single trial[70] that did not specify their source of support.

Populations. All but one study[60] used the NINCDS criteria to diagnose dementia. Eight studies included only AD patients, one study included only VaD,[68] and the remaining two included Parkinson's disease dementia (PDD[65]) and AD patients with cardiovascular disease.[64] A single

trial included subjects with Down's syndrome and AD.[60] The severity of the dementia patients was described as mild to moderate in five studies,[65,66,60,62,70] mild to moderately severe in two studies,[69,67] probable in two studies,[61,68] and moderate to severe in two studies.[63,64]

Some studies specified that the dementia patients were recruited from the community,[68,63,60] one study from institutional setting,[64] and the remaining did not specify the living arrangements. Mean ages of the study subjects ranged from 54 to 85.7 years with most studies representing ages in the upper to mid 70s.

Six studies [61,62,65,66,67,69] specified the race of the subjects, and of these, the overwhelming sample was Caucasian (range from 92 - 100%). All but one study[68] specified the proportion of men recruited, the range being from 18 - 46%. Four of these studies presented some results stratified by gender,[62] age,[64] APOE genotype,[62] baseline MMSE,[63,64] patients with Down's syndrome,[60] and the use of psychoactive drugs.[63] Three studies specified the baseline MMSE[61,64,70] demonstrating no differences between placebo and treatment group, and the mean values varied from 14 to 16.

Intervention. Five studies evaluated a 10 mg dose given once daily,[60,61,62,63,66] two studies 5 mg daily,[64,69] and four studies compared 5 mg and 10 mg dose groups.[65,68,67,70] Titration periods observed included 7 days[65,67] and 4 weeks,[70,68] these were not specified in the remaining studies. The total duration of the drug (including titration) varied from 12,[65] 15,[67] 23/24,[60,63,64,65,66,68] and 54/56[61,62] weeks.

Primary outcomes. Specific cognitive tests and caregiver burden were not evaluated in these studies. Nine studies used the MMSE, and six studies the ADAS-cog.

Analysis. All but one of the studies[60] comparing donepezil to placebo used ITT analysis. The study using OC analysis showed no statistical difference between treatments. It had the smallest sample size of 30 subjects and was underpowered (PW = 0.16) for the behavioral measure used, NPI.

Results and interpretation. See Summary Table 2. For the 10 trials[60,61,62,63,64,65,66,67,69,68] comparing donepezil to placebo, two studies[60,64] did not show a positive effect for the domain of general cognition. However, both of these studies evaluated the outcomes in this domain as secondary outcomes, with one trial[64] lacking sufficient power for the MMSE (PW = 0.69); for the other trial, power could not be evaluated. For the eight trials[61,62,63,64,66,69,67,68] showing a positive effect on general cognition, all but one trial used the MMSE as an outcome, which allowed for a pooled effect size estimate (Figure 5); we assumed that the VaD patients in one trial[65] could be combined with the other dementia populations. Figure 5 shows a consistent treatment effect for improvement in general cognitive function as measured by the MMSE, and the overall effect was statistically significant. Figure 6 shows the four trials[65,66,67,68] that used the ADAS-cog to measure general cognitive function change. A consistent effect favoring treatment was evident, and the test for overall effect was statistically significant. It should be noted that some of the values used in the pooled estimates for the MMSE and the ADAS-cog were derived from figures showing means and confidence intervals in the trial reports, thus introducing some imprecision into these estimates.

Figure 5. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the MMSE comparing donepezil and placebo.

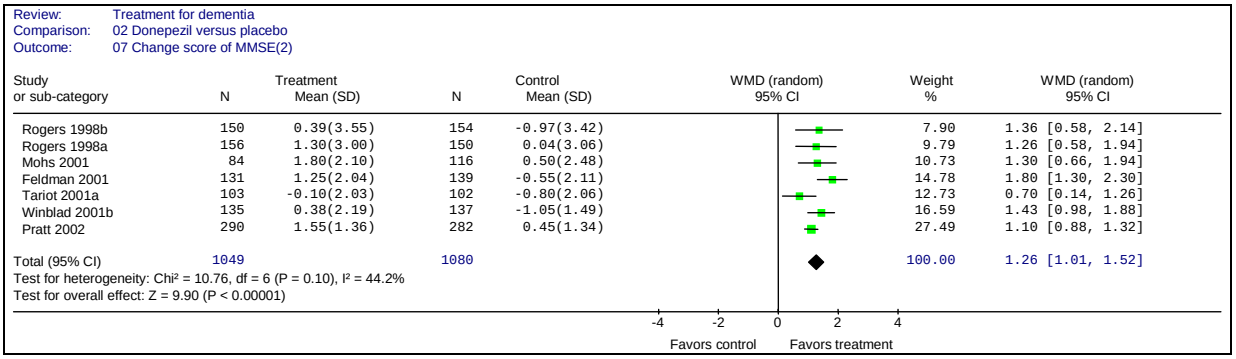
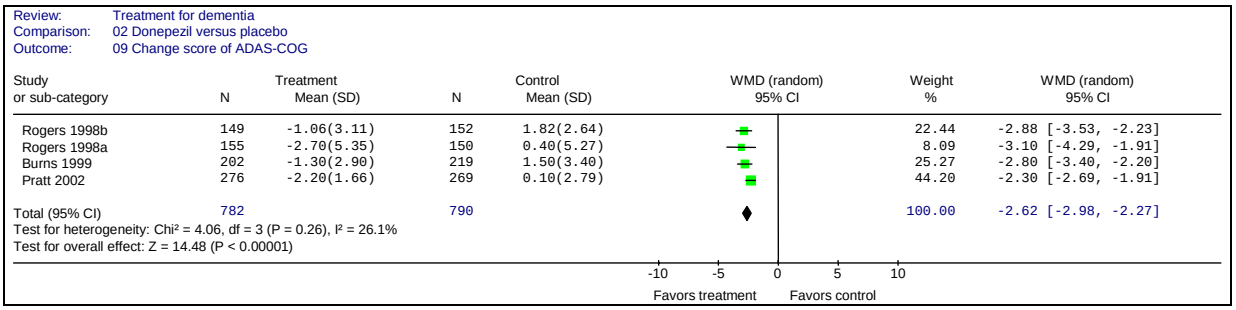


Figure 6. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing donepezil versus placebo



Ten studies[60,62,63,64,70,65,66,67,69,68] evaluated global assessment, and with the exception of three trials,[60,69,70] all studies showed a statistically significant difference in this domain. The overall effect for the CIBIC (Figure 7), and the CIBIC + (Figure 8, expressed as a proportion of improved versus not improved) were estimated for the 5 mg dose of donepezil. Figure 9 shows the summary estimate for the three studies[65,66,68] that evaluated the 10 mg dose of donepezil; heterogeneity was significant (p = 0.007) in this meta-analysis, but the overall effect was significant (p = 0.002). Similarly, Figure 10 shows the summary estimate for the Clinical Dementia Rating (CDR) global assessment measure. A radial plot of these three studies was undertaken and suggests that one trial[64] could be an important source of the heterogeneity. Summary estimate was also calculated for the Neuropsychiatric Inventory (NPI), which was classified in the behavior domain. It was noted that two of the three studies that evaluated this outcome were lacking sufficient power[60,64] (PW = 0.11, PW = 0.16). The test for heterogeneity was significant but the test for overall effect was not. Thus, the results of the summary estimates for the NPI outcome are problematic. Two global assessment outcomes, the CIBIC+ and the CDR, show a consistent effect favoring the drug treatment at 5 mg; the evidence is inconsistent for the 10 mg dose.

Figure 7. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the CIBC+ (continuous data) comparing donepezil versus placebo

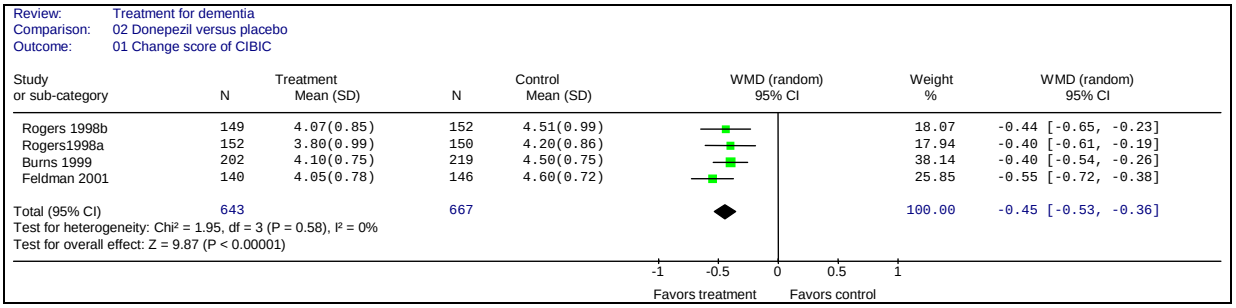


Figure 8. Relative Risk (RR) from the Random Effects Model (Random) for the CIBIC+ (dichotomous data probability of improving) for a 5 mg dose of donepezil.

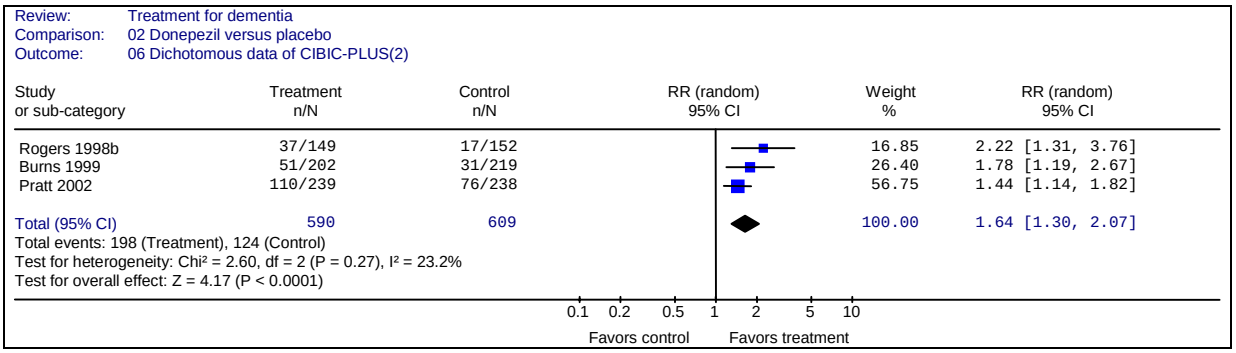


Figure 9. Relative Risk (RR) from the Fixed Effect Model (fixed) for the CIBIC+ (dichotomous data [improved versus not]) for a 10 mg dose of donepezil.

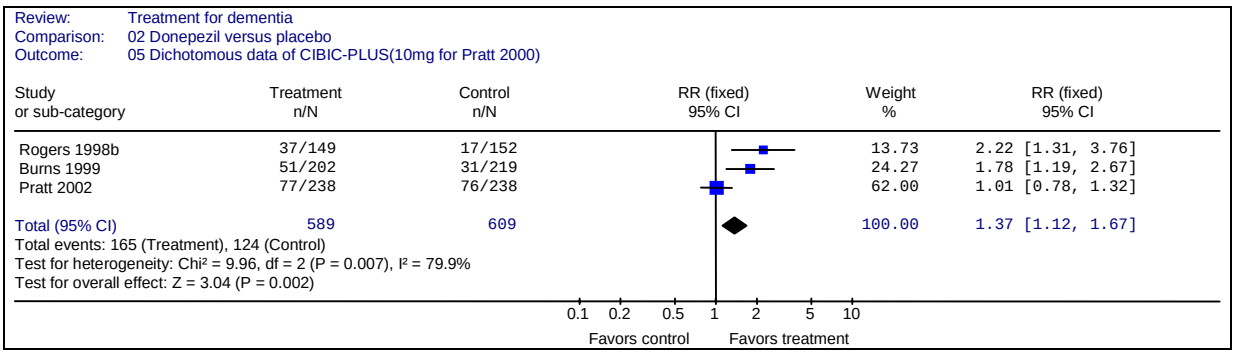
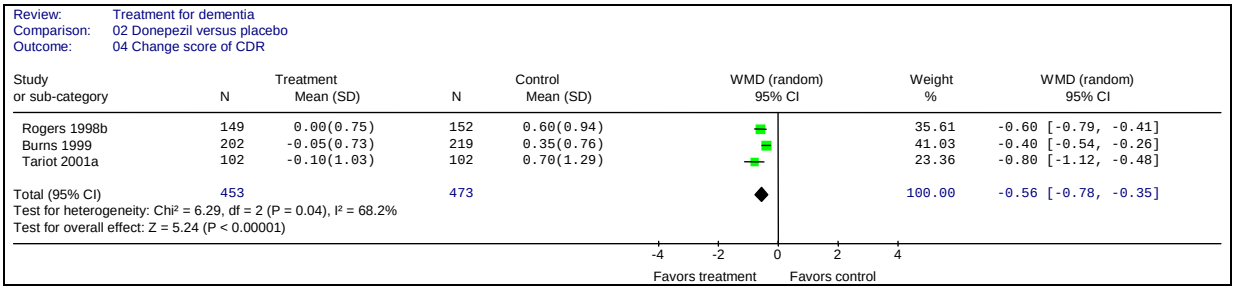


Figure 10. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the Clinical Dementia Rating (CDR) comparing donepezil versus placebo.



Five of the eight studies[60,61,63,64,65,66,67,69] measuring Activities of Daily Living (ADL) found a significant difference in the various outcomes used to assess ADL, but none of these could be combined into a summary estimate. It should be noted that the majority of trials selected these ADL variables as secondary outcomes. Behavior outcomes were not significant or showed mixed results for the three studies that evaluated this domain but these lacked sufficient power. Only one study collected caregiver stress and health service utilization outcomes[63] but did not report these data.

Quality scores for reporting adverse events varied from 1 to 4 but the majority of trials scored 3 or greater (n=7). One recently published study[68] scored 1, with no events detailed. Withdrawal due to adverse events ranged from 0 - 18% for treatment groups and 0 - 11% for placebo (see Evidence Table 21). Four studies[65,68,67,66] were able to demonstrate a dose effect, with increasing frequency of events as dosage increased. One study[62] reported significant differences between treatment and placebo for balance problems and asthenia (neurological fatigue). Fatigue was shown to be significant in two other studies.[61,66] Four [65,61,66,67]out of six studies testing differences between groups were statistically significant for diarrhea (placebo = 3 - 21%, all doses donepezil = 0 - 38%), nausea and vomiting (placebo = 4 - 9%, all doses donepezil = 4 - 25%). The other a priori symptom reported was agitation and frequencies for placebo varied from 0 - 8% and for all doses from 3 - 19%; but these were not shown to be statistically different. No serious adverse events requiring hospitalization were reported or shown to differ statistically between groups.

Galantamine. See Evidence Tables 22 through 29 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Six studies of galantamine[71,72,73,74,75,76] were included in this review. All compared galantamine with placebo and were published between 2000 and 2002 (from six different authors).

Design/methodology. The sample sizes for subjects ranged from 285[73] to 978[74] with 3530 subjects evaluated in total. All quality scores were high, with either 7 or 8 on the Jadad scale. Funding sources for these studies varied; one study did not report funding source,[74] one was funded by a non-industry source,[75] one was partially funded by industry,[71] and three were funded by industry.[72,73]

Populations. All but one of the studies[71] included AD patients only, and this single study mixed VaD and AD patients. All subjects in these studies were classified as mild to moderate.

One study specified that the subjects were from the community.[73] All studies included from 36 - 53% male subjects, and the mean age ranged from 72.2 to 76.8 years. Three studies[71,74,76] specified race, and with the largest proportions being white (range from 91.5 - 99.9%). Two studies evaluated subgroups, based on baseline MMSE[75] and APOE genotype.[75,76]

Intervention. All studies had a titration period, starting at 4 mg per day[71,73] or 8 mg per day.[72,74,75,76] Four studies increased the dose weekly,[71,72,75,76] and one study increased every 2 to 3 days.[73] All studies had a treatment dose of 24 mg per day. Three studies[73,75,76] included other doses ranging from 16 mg per day to 36 mg per day. Trials were undertaken for a minimum of 3 and maximum of 6 months.

Primary outcomes. All domains were measured except for specific cognitive tests and caregiver burden. All studies used the ADAS-cog and CIBIC or CGIC measures as primary outcomes. None reported baseline mean MMSE values.

Analysis. All but one[71] of the studies reported ITT analysis, and the results of this study did not differ from the others.

Results and interpretation. See Summary Table 3. Five of the six trials[71,72,73,74,75,76] that evaluated general cognitive function showed a significant effect. One trial[73] showed mixed effects with the ADAS-cog showing some improvement at the 24 mg but not the 32 mg dose level . Figures 11 and 12 show the pooled estimate for the ADAS-cog for five studies for 24 and 32 mg doses; one trial[71] was excluded from the pooled estimate as the population of this study was thought to be a source of heterogeneity. However, the test for heterogeneity for the 24 mg dose (Figure 11) was significant (p = 0.001) despite omitting this study, but the overall effect was significant (p = 0.0005); this estimate should be interpreted with caution. The pooled estimate for the 32 mg dose (Figure 12) showed a consistent effect favoring treatment and was significant (p < 0.00001).

Figure 11. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing galantamine at 24 mg dose versus placebo.

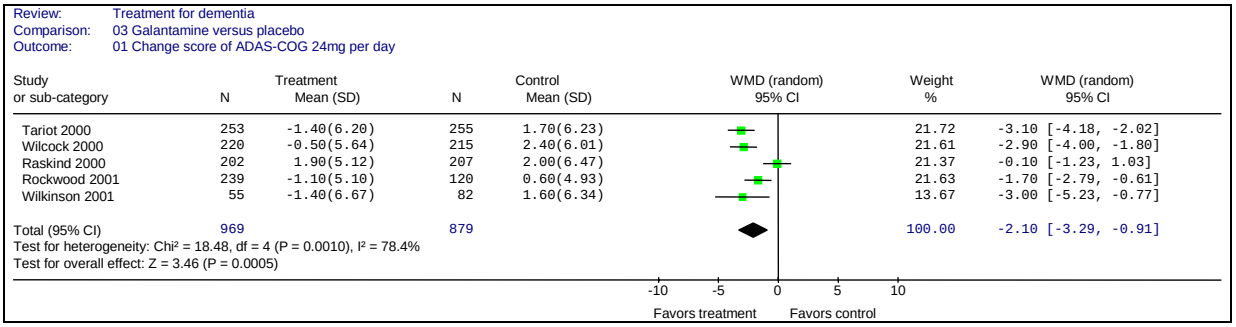
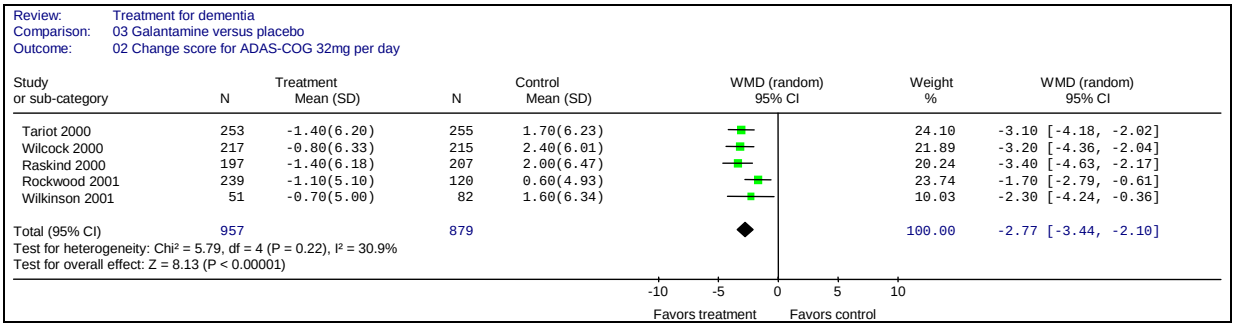


Figure 12. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing galantamine at 32 mg dose versus placebo.



All studies evaluated global assessment with the CIBIC+ with one exception.[73] All studies with the exception of this study showed a significant difference between placebo and treatment for both the 24 and 32 mg doses. Figures 13 and 14 show the pooled estimates for the CIBIC+ for these two dosages and suggest an overall effect size of equivalent magnitude for either dose. Similarly, all studies evaluated quality of life/ADL with a variety of different outcome measures; four studies[71,72,74,75] showed statistically significant differences between groups, and two studies did not.[76,73] Figures 15 and 16 shows the results of pooling the estimates for the Disability Assessment for Dementia (DAD)[77] outcome in those studies that provided sufficient data. In this instance, we included the trial with mixed dementia populations[71] to have a minimum of three studies required for a pooled estimate. A consistent, statistically significant effect favoring treatment is evident; the higher dose of 32 mg shows a slightly larger effect size relative to 24 mg. Two of the three studies that reported on behavior/mood outcomes showed statistically significant differences (Summary Table 3).

Figure 13. Relative Risk (RR) from the Random Effects Model (Random) for the CIBIC comparing galantamine at 24 mg dose versus placebo.

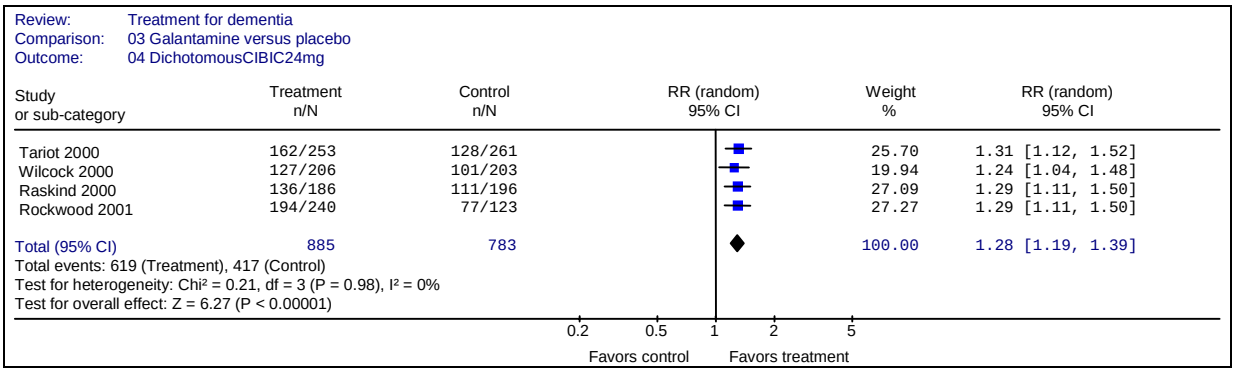


Figure 14. Relative Risk (RR) from the Fixed Effects Mode Fixed l for CIBIC comparing galantamine at 32 mg dose versus placebo.

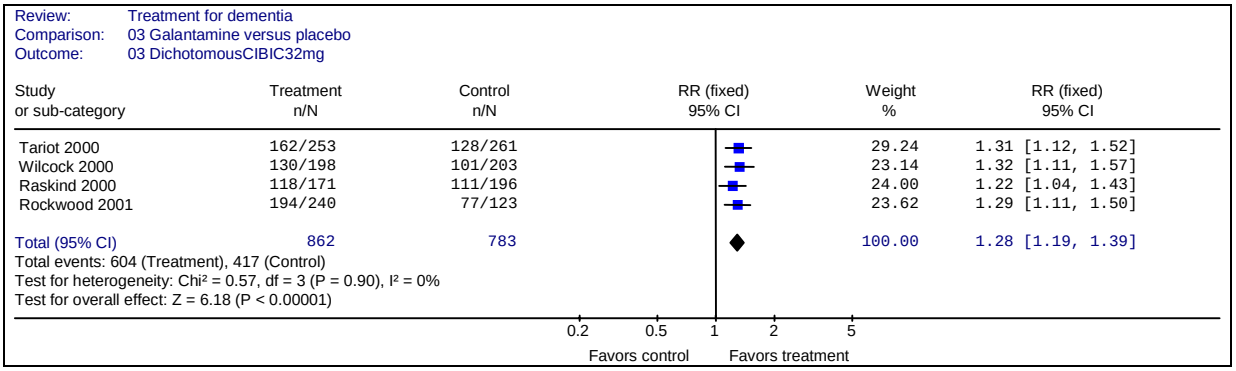


Figure 15. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the DAD comparing galantamine at 24 mg dose versus placebo.

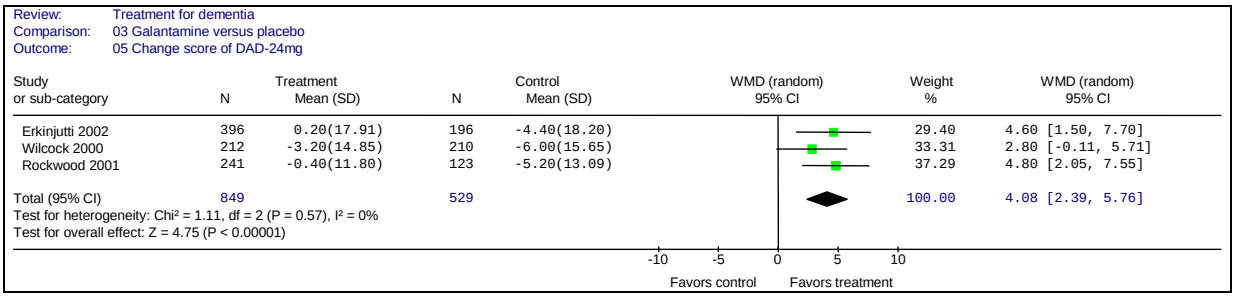
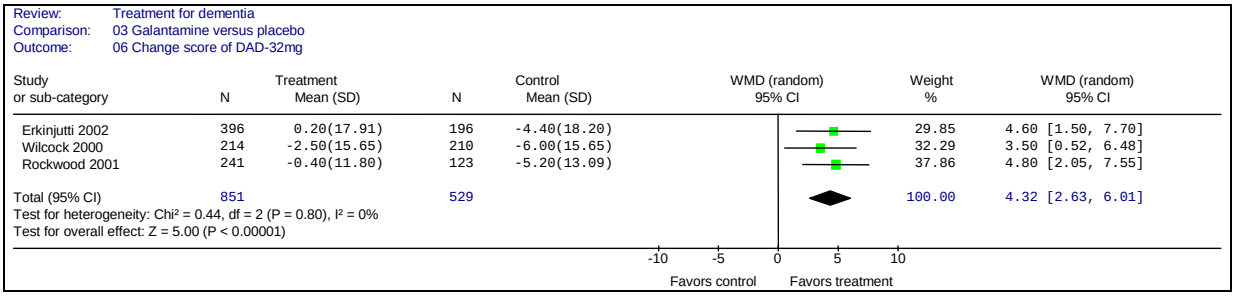


Figure 16. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the DAD comparing galantamine at 32 mg dose versus placebo.



Five[71,73,74,75,76] of the six trials scored 3 out of 5 on our quality scale for rating adverse events. One trial[72] scored 4. Withdrawal rates due to adverse events ranged from 4 – 9% for placebo and 8 – 27% for the treatment group. One study[73] showed a dose response for adverse events. Although, most trials did not report testing for differences between groups, two trials[76,75] reported a statistical significant difference in weight loss between the placebo and treatment group. Statistical differences for aberrant hematology were not significant in any of the five studies that evaluated this (Evidence Table 29). The most common types of adverse events reported were gastrointestinal symptoms (nausea and vomiting, diarrhea), eating

disorders/weight loss, and dizziness (four studies, see Evidence Table 29). The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea and vomiting (placebo = 3 - 13%, all doses = 6 - 44%), 2) dizziness (placebo = 3 - 11%, all doses = 4 - 19%), 3) diarrhea (placebo = 2 - 10%, all doses = 4 - 19%), 4) agitation (placebo = 1 - 9%, all doses = 6 - 15%), and 5) eating disorder (placebo = 0 - 6%, all doses = 4 - 20%).

Metrifonate. See Evidence Tables 30 through 40 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Nine studies[78,79,80,81,82,83,84,85,86] were eligible for this systematic review. Studies were published from 1996 to 1999, and all studies compared metrifonate to placebo.

Design/methodology. Overall, 2759 subjects were evaluated. Sample sizes randomized ranged from 27 to 605 subjects. Quality of the studies ranged from 5[80] to 8,[81] with the majority of studies earning 6 points.[82,83,79,85,78] Two studies were non-industry–funded[78,79] and one did not specify the source of funding,[80] while the other six studies were partially or wholly funded by industry.

Populations. The subjects in all included trials were classified as having mild to moderate AD. Not all trials specified the source of recruitment or the racial composition of subjects. Three studies specified a community sample,[86,79,85] and three trials reported the racial composition l,[83,86,84] which was greater than 90% white in all cases. Mean age for all of the studies ranged from 71.4 to 75.0 years, with one study not reporting the mean age.[80]

Intervention. All but one study[86] reported the loading dose, which varied from 0.5 mg per kg to 5.0 mg per kg. Following this initial loading period, the maintenance dose varied from 0.65 mg per kg to 4 mg per kg and 50 mg per day. The duration of the study treatments varied from 21 days to 26 weeks.

Primary outcomes. All outcome domains were evaluated with the exception of caregiver burden. ADAS-cog, CIBIC+, and MMSE were most frequently used as outcomes.

Analysis. Four trials reported OC analyses[78,79,80,85] and the remaining reported ITT analyses.

Results and interpretation. See Summary Table 4. A consistent positive change in cognitive function was found in all studies that reported this outcome (n = 8). One study[85] tested cognitive function, global assessment, and behavioral outcomes and reported the baseline endpoint scores but did not test for differences between treatment and placebo groups. Four of the eight studies reporting global assessment outcomes showed statistically significant differences between groups, and two[83,86] showed mixed results. The remaining two trials showed no significant results for global assessment, but they were secondary rather than primary outcomes. All studies that evaluated behavior/mood and quality of life/ADL outcomes (with the exception of one trial[86]) showed no significant findings or mixed findings; it should be noted that all were secondary outcomes. There were not enough similar outcomes reported to complete a pooled analysis for metrifonate.

With the exception of a single study, quality scores for reporting adverse events were greater than 3 and generally well reported. However, only one trial [83] tested for differences between

groups and found nausea and vomiting, diarrhea, and muscle and joint disorder to be significantly different. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea and vomiting (placebo = 3 - 14%, all doses = 2 - 50%), 2) dizziness (placebo = 1%, all doses = 3 - 4%), 3) diarrhea (placebo = 4 - 14%, all doses = 11-19%), 4) agitation (placebo = 2 - 14%, all doses = 8 - 33%), and none reported eating disorder as an adverse event. Withdrawal rates due to adverse outcomes varied from 0 – 9% for placebo and 0 – 12% for treatment groups. Some studies indicated arrhythmia[80,82,83,85] and hypotension[82,85] and hematological abnormality[82] but did not test for differences between groups. The majority of studies reported that laboratory tests including liver function and hematology were within normal limits. Overall, it was difficult to determine which types of adverse events reported had the potential to cause serious harm. This is some concern as metrifonate is no longer used as a therapy for dementia due to its potential for serious adverse events that include: respiratory paralysis, bradychardia, severe leg cramps and dyspepsia.[87]

Nicergoline. See Evidence Tables 41 through 47 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Four studies[88,89,90,91] compared the effect of nicergoline to placebo, and one study,[92] published in 1994, compared nicergoline to antagonic-stress. The four placebo comparison studies were published in 1995,[91] 1997,[89,90] and 2001.[88]

Design/methodology. Sample sizes in the controlled studies varied from 108 to 346, with the total number of subjects included totaling 705. The drug versus drug study had only 62 subjects. The placebo trials all had quality scores of 6 points, while the non-placebo trial had a quality score of 5. Funding sources were reported only in two studies,[88,90] and both were industry-funded.

Populations. These studies had a very mixed population of dementia patients. Two included AD only,[88,92] one trial MID only,[89] one trial included both senile dementia of Alzheimer type (SDAT) and MID,[91] and one trial included PDD, VaD, and mixed dementia.[90] All subjects had mild to moderate dementia. Studies included 38 - 55% male subjects; one study[91] did not report the gender proportions. Mean age of subjects ranged from 69.3 to 73.7 years with one study not reporting[91] this value. One study[91] compared SDAT patients to MID patients.

Intervention. All trials versus placebo used 60 mg per day, but duration varied from 2 months,[91] 6 months,[88,89,92] and 12 months.[90]

Primary outcomes. Caregiver burden was the only domain not evaluated by at least one of the studies. Three trials[89,90,91] specified baseline MMSE, and this varied from 20 to 22.

Analysis. Two of the trials reported OC analyses[90,91] and two reported ITT analyses[89,88]; the trial comparing nicergoline to antagonic-stress presented OC analysis only.

Results and interpretation. See Summary Table 5. There was a consistent positive effect for improvement in general cognitive function as all four studies showed a statistically significant difference. The evidence for benefit in the global assessment domain is inconclusive as only two of the trials[89,90] found significant differences and two trials[88,93] had mixed results (see Summary Table 5). Two trials[91,88] measured behavior/mood and found no significant difference. A single

trial[88] evaluated quality of life/ADL; although two outcomes in this domain were used (both as secondary measures), none was significant relative to placebo. There were not enough similar outcomes reported to complete a pooled analysis for nicergoline.

Quality scores for reporting adverse events varied from 2 to 5 for these four trials, and none tested for differences between groups. Withdrawal due to adverse events varied from 0 – 8% for placebo and 0 to 9% for the treatment group. The trial with the lowest quality reporting score [89] reported the most number of different events (up to 23 event types). With the exception of headache, which was reported in all four trials, it was difficult to determine which types of adverse events most characterized exposure to this pharmacological agent. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = 3%), 2) dizziness (placebo = 1 – 2%, all doses = 0% or not reported), 3) diarrhea (placebo = 2 - 6%, all doses = 2 - 4%, 4) agitation (placebo = 5%, all doses = not reported), and none reported eating disorder as an adverse event.

Physostigmine. See Evidence Tables 48 through 53 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Four studies were eligible for our review,[94,95,96,97] all comparing physostigmine to placebo only. The studies were from 1996, 1999, and 2000 with two of the studies being by the same author.[95,96]

Design/methodology. Sample size ranged from 176[97] to 475[96] with an overall total of 1198 subjects. Quality scores were 5,[96] 6,[94,95] and 7[97] out of 8 possible points. Two studies were industry-funded,[97,96] one was partially funded by industry,[95] and one did not report funding source.[94]

Populations. All subjects had a diagnosis of mild to moderate or probable AD. Only one study[96] reported that all subjects were drawn from the community. Mean age ranged from 68.6 to 73.4 years, and the proportion of male subjects varied from 39.8 - 63%.

Intervention. Treatment schedules varied across the studies. One study[94] used a patch (30 and 60 mg), one trial used 30 mg (15 mg twice daily),[97] one trial had a washout and titration every 3 weeks to 30 or 36 mg per day,[96] and another trial titrated weekly to 15 mg twice daily.[95] Duration of treatment ranged from 6 weeks[95] to 24 weeks.[94,96]

Primary outcomes. All studies used the ADAS-cog as a primary outcome, and none reported caregiver burden or behavior/mood measures. No studies reported baseline MMSE scores.

Analysis. All but one trial[94] used ITT analysis.

Results and interpretation. See Summary Table 6. Although all four trials measured general cognitive function, only three reported the results. All of these were statistically significant (see Summary Table 6) for the ADAS-cog, with change scores varying from 0.95 to 2.9 (change from baseline). Two trials [95,96] found significant change for global assessment outcomes; the remaining two showed mixed results[97] and non-significance.[94] Behavior/mood was only measured in one trial,[94] and the effect was not reported. Three of the trials included measures of

quality of life/ADL as secondary outcomes[95,96,97] and all found no significant difference from placebo but these were secondary outcomes and may reflect a lack of power. There were not enough similar outcomes reported to complete a pooled analysis for physostigmine.

The quality scores for reporting adverse events were generally low, scoring 1 or 2 out of 5. Withdrawal rates due to adverse events varied from 1 - 5% for placebo and 12 - 55%in the treatment group, with one study[97] not reporting rates. The high withdrawal rates were in studies with sample sizes that varied from181 to 475 subjects. A single study[97] tested for differences between groups, and found that dizziness, tremor, weight loss, asthenia (varying from 6 - 22% for all doses), confusion, delirium, and respiratory problems were significantly different. The cluster of reported types of adverse events suggests that gastrointestinal problems (abdominal pain, diarrhea) (placebo = 1 - 9%, all doses = 13 - 28%), nausea and vomiting (placebo = 1 - 9%, all doses = 9 - 75%) and eating disorder (placebo = 2 - 6%, all doses = 5 - 16%) were most frequently reported. Dizziness (placebo = 4 - 13%, all doses = 11 - 38%) and agitation (placebo = 6 - 16%, all doses = 4 - 8%) were also reported. No events deemed serious enough for hospitalization were reported.

Posatirelin. See Evidence Tables 54 through 59 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Four studies[98,99,100,101] compared posatirelin to placebo, and one of these [101] also compared it to citicoline. One study was published in each of the years from 1995 to 1998, and all studies were conducted in Italy. Two studies were by the same author.[100,101]

Design/methodology. Populations randomized in the studies varied from 136[100] to 360[99] with a total of 931 in all trials. Quality scores ranged from 5[98] to 7[100] out of a possible 8 points. Three of the four studies did not report the source of their funding, but one trial[100] reported partial funding by industry.

Populations. No two studies included exactly the same populations; one trial had only AD,[101] one trial had only VaD,[100] one trial had mixed AD and VaD,[99] and another trial had mixed AD, VaD, and PDD.[98] This latter trial[98] compared populations in a subgroup analysis of AD versus VaD. All studies evaluated populations with mild to moderate disease.

The mean age of the subjects ranged from 69.4[100] to 78.8[98] with the percentage of male subjects varying from 34[101] to 66%.[100] One study[100] included a dementia population who also had hypertension.

Intervention. A dose of 10 mg per day was used in all studies, and treatment interval varied from 3 to 4 months.

Primary outcomes. General cognitive function was evaluated in all studies using the intellectual impairment Gottfries-Bråne-Steen (GBS) subscale and the MMSE was used in one trial.[101] Specific cognitive function was evaluated in one trial.[100] Quality of life/ADL was evaluated with the ADL subscale of the GBS, and behavior/mood was evaluated with the emotional impairment subscale of the GBS. GBS total score was assumed to be a measure of quality of life/ADL rather than global assessment. None of the trials reported baseline MMSE scores.

Analysis. Two of the studies[100,101] used OC analysis to report outcomes.

Results and interpretation. See Summary Table 7. All four studies evaluated general cognitive function, and three of these trials[100,99,98] reported significant differences using the intellectual impairment subscale of the GBS as a measure of this attribute. One study[100] measured this same outcome and the MMSE, but did not report results for the latter outcome. One study[101] measured reported changes within a treatment relative to baseline and not relative to placebo; this study demonstrated superiority for posatirelin relative to citicoline (a third comparison group), but did not test for differences between the placebo group. Showing non-inferiority of citicoline in this trial does not establish efficacy with respect to placebo. Statistically significant changes were also shown for the domain of quality of life/ADL as measured by the GBS total score or GBS ADL (FactorII) subscales in three of the studies.[98,99,100] A single trial[100] evaluated global assessment using the TP Global scale in VaD subjects. There were not enough similar outcomes reported to complete a pooled analysis for posatirelin.

Quality scores for reporting adverse events varied from 2 to 4. Withdrawal rates due to adverse events ranged from 0 - 3%in placebo and 0 - 4%in the treatment group. One trial[100] did not report the rate of withdrawal. None of the studies tested for significant differences between groups. All studies reported the presence of agitation, and at least three studies reported arrhythmia, nausea/vomiting, headache, rash/skin disorder, and sleep disorder; there is no evidence to suggest that these differed between placebo and treatment group. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = 1 - 4%), 2) dizziness (placebo = not reported, all doses = 1%), 3) diarrhea (placebo = 2%, all doses = 2%), 4) agitation (placebo = 1 - 5%, all doses = 1 - 5%), and none reported eating disorder as an adverse event. No serious adverse events were reported.

Rivastigmine. See Evidence Tables 60 through 67 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Six studies were eligible for this review, all comparing rivastigmine to placebo. Studies were published in 1998,[102,103] 1999,[104,105] 2000,[106] and 2001.[107]

Design/methodology. Six studies evaluated 2071 subjects in total, with studies ranging from 27[107] to 725[104] subjects. The quality of studies varied from 5 to 8, with three studies[106,104,103] scoring 8 points and one[107] earning 5 points. All studies were funded by industry sponsors.

Populations. Four studies were evaluated in AD patients,[107,105,104,103] one trial[102] dementia of the Alzheimer's type (DAT), and one study[106] Lewy body dementia subjects for mild to moderately severe subjects. One study[103] reported a subgroup analysis by vascular risk. One study reported a community sample in their trial.[104] Mean age for the studies ranged from 69.4[102] to 75.9 years.[107] Two studies[107,105] did not report the ratio of male subjects in their study, and the other four varied from 39 - 56%. One trial[104] reported co-morbidity of diabetes, hypertension and arthritis; one trial[103] reported concurrent medication use for cardiovascular, gastrointestinal and analgesic aids.

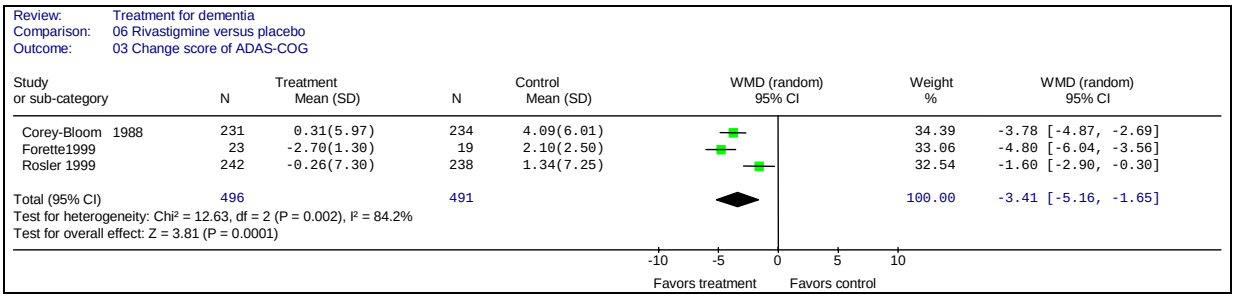
Intervention. Doses for rivastigmine varied from 1 mg[103] to 12 mg,[106,105,104] and treatment duration varied from 14[104] to 26[107,103] weeks. All studies titrated the dose of drug over a period ranging from 2 weeks[106] to 12 weeks.[107]

Primary outcomes. The ADAS-cog and CIBIC+ were evaluated in half the studies. Baseline MMSE was reported in two trials,[103,106] and the mean scores varied from 18 to 20. Specific cognitive function, behavior/mood, and quality of life/ADL were infrequently evaluated, and caregiver burden was not evaluated in the trials.

Analysis. Trials were evenly divided between ITT analyses[106,104,103] and OC.[107,105,102]

Results and interpretation. See Summary Table 8. Although, general cognitive function was evaluated in five studies, only four reported findings, which were all statistically significant; one of these was borderline significant (p = 0.054) (see Summary Table 8). Two of these studies[104,103] represented two sites (North American and European) of the same protocol. Although the same protocol was used, one study[103] found significance for both high (6 – 12 mg) and lower (1 – 4 mg) dosages, but the other trial did not show significance for the lower dose, likely due to lack of power for this outcome (PW = 0.67). Interestingly, at the 12-week midpoint, the low dose groups in both these studies appeared to be worse than placebo for all primary outcome measures, but then migrated to improvement at the 26-week endpoint. For those studies[105,104,103] that reported ADAS-cog change scores from baseline for the treatment group, mean change values varied from -2.75 to 0.26. Figure 17 shows the pooled estimate for those trials that provided sufficient data and represents the 12 mg dose. However, the test for homogeneity was significant suggesting that the pooled estimate should be interpreted with caution (albeit a significant overall effect). For those studies that reported MMSE change scores from baseline for the treatment group, mean values varied from 0.0 to 0.6; a single trial[103] showed a decline of 7.9 points relative to baseline for the placebo after 26 weeks (other trials reporting MMSE scores did not report such marked change).

Figure 17. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing rivastigmine versus placebo.

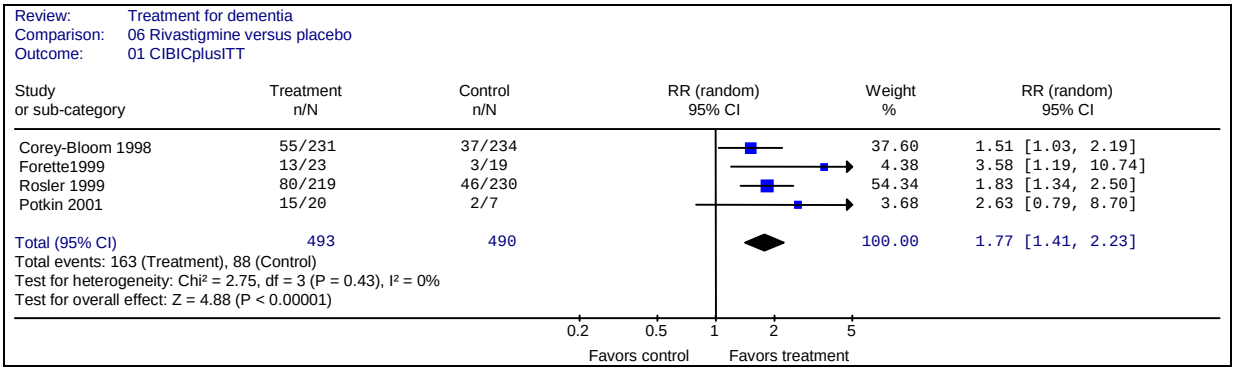


Two trials evaluated specific cognitive tests; one trial[106] showed statistical significance for the CCASSS but not for the MMSE (general cognitive test). Similarly, another trial[105] found the Weschler Logical memory (instant recall) to be significant but the ADAS-cog (general cognitive outcome) was borderline significant.

With respect to global changes, five of six studies showed significant changes, and from these, three studies[104,103,102] were for the high dose only. One of these studies[102] defined the high dose as 6 mg per day, which was the minimum dose level for the other two studies. One study[107] showed a statistical difference for the two deterioration categories (5 – 7) in the CIBIC+, but not in the improvement categories when comparing treatment and placebo groups. Figure 18 shows

the pooled estimate for the CIBIC+ in those studies that provided sufficient information. A consistent effect favoring treatment is shown, but the two smaller trials display large confidence intervals (Figure 18). There was no clear trend in the domains of behavior/mood and quality of life/ADL as not all studies evaluated these domains.

Figure 18. Relative Risk (RR) from the Random Effects Model (Random) for the CIBIC+ comparing rivastigmine versus placebo.



Quality scores for reporting adverse events varied from 2 to 5. Withdrawal rates due to adverse events ranged from 4 - 11% in the placebo and 11 - 27% in the treatment group. One trial[107] did not report the withdrawal rates or the types of adverse events observed. Two trials[103,104] demonstrated a dose response; however, one of these trials[104] showed significant differences for nausea and vomiting only, and the other trial[103] showed significant for all the adverse events reported. With respect to the types of adverse events, the majority of studies reported dizziness, nausea and vomiting, eating disorder/weight loss, and headache. It should be noted that one study[105] allowed intentional prescribed anti-emetic drugs to increase the tolerance of subjects taking rivastigmine. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3 - 10%, all doses = 8 - 58%), 2) dizziness (placebo = 0 – 7%, all doses = 6 – 20 %), 3) diarrhea (placebo = 2 - 9%, all doses = 7 - 17%), 4) eating disorder (placebo = 4 – 8%, all doses = 4 – 19%), and 5) agitation was not reported. No serious adverse events were reported.

Tacrine. See Evidence Tables 68 through 77 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Eight studies evaluating tacrine were eligible for this review; tacrine was compared to placebo in six trials[108,109,110,111,112,113] (lecithin was assumed to be like placebo) and to other drugs in two trials.[114,26] One study[114] compared two arms with tacrine, one with silymarin added and one placebo arm. The other non-placebo controlled trial compared tacrine with idebenone.[26] These drug versus drug trials were published in 1999 and 2002. The placebo controlled trials were published 1991,[111] 1994,[108,109,113] 1996,[110] and 1999.[112]

Design/methodology. The placebo studies evaluated 994 patients in total with a range of 13[111] to 663[108] subjects per study. Quality scores out of 8 points were evenly distributed with two studies each having scores of 5, 6 and 7. Both drug versus drug trials had scores of 7. One study[109] was not funded by industry, and one trial[114] did not report its source of funding; the other six studies had at least partial, if not full, industry support.

Populations. All studies included AD subjects; one trial[26] also included PDD patients. Subjects in all studies had mild to moderate or probable disease. Five of the studies[113,109,111,114,26] reported that their sample was from the community. The mean age ranged from 68[110] to 75 years,[113] and the percentage of male subjects in the studies varied from 13[110] - 54%.[113] One study reported race with 100% white subjects.[26]

Intervention. See Summary Table 9. All placebo-controlled trials used a titration period to get to maximum dose, from 11 days[113] to 18 weeks.[112,108] Treatment doses varied from 80 mg per day[110] to 160 mg per day.[108] Treatment duration was either 12/13 weeks,[110,113,111] or 30/36 weeks[112,108,109] for all placebo-controlled studies. The trial versus Idebenone[26] was for 60 weeks and the trial with silymarin[114] was for 15 weeks.

Primary outcomes. All six of our identified domains were evaluated by at least one trial. All trials measured cognition; however, sufficient data to permit pooled analyses could not be adequately abstracted from all these studies that had similar outcomes. Baseline MMSE varied from 14 to 18 in the fours trials[112,110,109,114] that reported this.

Analysis. Five studies[108,112,113,114,26] reported ITT analysis and three did not.[109,111,110]

Results and interpretation. Of the six placebo-controlled studies, only one trial[108] showed statistical significance for general cognitive function as measured by the ADAS-cog (ES = −0.268). Three doses (80 mg,120 mg,160 mg) were compared in this trial, and the 120 and 160 mg per day were shown to be statistically significant (approximately a mean change of 2 points on the ADAS-cog). One trial[112] showed mixed results for the two outcomes used (CASI and MMSE) to evaluate general cognitive function; this trial was underpowered for both these outcomes (PW = 0.22 and 0.26, respectively). Three trials[109,110,111] found no statistical differences between treatment and placebo but had small sample sizes, ranging from 12 to 32 subjects, and were likely underpowered (insufficient reporting to estimate power). A fourth trial[113] also found no statistical difference (p = 0.55) for general cognitive function, but the study duration was 12 weeks. It should be noted that this study used an 80 mg dose, which was shown to have no benefit relative to higher doses of 120 and 160 mg.[108] A single trial[109] of small sample size evaluated specific cognitive tests and did not show statistical differences.

Three studies evaluated global assessment, and two [113,108] found statistical significance; the trial showing no benefit[112] also showed inconclusive findings for general cognitive function as well (PW = 0.05 for the CGIC). Four trials[108,109,110,113] evaluated behavior/mood and showed no difference between groups. Two trials[109,111] with small sample sizes measured quality of life/ADL and showed no significant changes; lack of sufficient power cannot be ruled out. There were not enough similar outcomes reported to complete a pooled analysis for tacrine.

The quality scores for reporting adverse events varied from 1 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0 - 12% for placebo and 0 - 55% in the treatment group. The higher rates of withdrawal were associated with higher doses. Elevated alanine transaminase (ALT) or hepatic abnormality (placebo = 4 - 13%, all doses = 7 - 67%) was reported in six studies, suggesting the potential for serious liver damage. None of these trials tested for differences between treatment and placebo with respect to adverse events. Five of the

studies reported nausea and vomiting (placebo = 0 - 9%, all doses = 9 - 37%); gastrointestinal problems and dizziness (placebo = 0 - 16%, all doses = 4 - 14%) was also noted in several studies. Frequencies of other a priori symptoms of interest are as follows: 1) agitation (placebo = 5 - 12%, all doses = 5 - 9%), and 2) diarrhea (placebo = 0 - 13%, all doses = 4 - 18%).

Velnacrine. See Evidence Tables 78 through 82 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Three studies evaluated velnacrine versus placebo, and these were published in 1991,[115] 1995,[116] and 1996.[117]

Design/methodology. A total of 774 subjects were studied with sample sizes ranging from 16[115] to 449.[116] Quality scores out of a possible 8 points varied from scores of 6[117,115] or 7.[116] All studies were sponsored by industry.

Populations. The characteristics of the populations all included probable AD subjects. The mean age of the participants ranged from 70.5 to 72.8 years and the percentage of male subjects ranged from 31 - 41%. Location of recruitment was not specified.

Intervention. The doses given for this drug overlapped between the studies, but they were on different schedules (once, twice, or three times per day). None of the studies had a titration period. One study[117] compared four doses (three daily doses of 10 mg, 25 mg, 50 mg, and 75 mg). One study[116] compared doses of 150 mg or 225 mg per day. The other study used a dose of 100 mg twice daily and had the smallest sample size.

Primary outcomes. General cognitive function was evaluated in all studies with the ADAS-cog, and none specified baseline MMSE values. A variety of outcomes were used to evaluate global assessment. At least one of these trials evaluated the other outcomes domains

Analysis. Only one of the trials[116] used an ITT analysis.

Results and interpretation. See Summary Table 10. One[115] trial was of very small sample size (n = 16) and of a 2 weeks duration, compared to the other two studies[117,116] with 15 or 24 weeks. Similarly, this trial evaluated two outcomes (specific cognitive function and global assessment) and showed mixed or non-significant results, likely a function of being underpowered. The two remaining studies[117,116] had sample sizes over 300 subjects and showed statistical significance for the domain of general cognitive function using the ADAS-cog. The magnitude of the change reported varied from –2.0 at 12 weeks and then –1.0 [116] at 24 weeks for the 225 mg dose group only; a mean change of 2.15[117] for the 75 mg (three times daily) as observed at the study endpoint of 15 weeks (no other dosage group was reported for this study). The trial[116] evaluating doses of 150 and 225 given once daily showed significant changes for 225 mg per day but not for 150 mg per day at endpoint (24 weeks), whereas, the trial with 75 mg twice daily did show significant change for general cognitive function.

All studies included assessment of global functioning, for which two[117,116] found significant differences, and one[115] had mixed results. Behavior/mood was evaluated in only one study[117] as a secondary outcome with an OC analysis, and no significant effect was found. Similarly, quality of life/ADL was measured in two studies as secondary outcomes, which produced opposite

results (not significant[117] and significant[116]). One of the trials[116] measured effects on caregiver burden as a secondary outcome and found a significant effect. There were not enough similar outcomes reported to complete a pooled analysis for velnacrine.

Quality scores for reporting adverse events were 3 for all studies. Withdrawal rates varied from 0 - 22% for the placebo group and 5 - 33% for the treatment group. None of the studies reported a dose response. None of the studies tested for statistical differences between the placebo and treatment groups. Two studies reported aberrant hematology and hepatic abnormality[116,117]; for these two studies the rate of occurrence were 2 - 21% for placebo, and 32 - 40% for all doses. All studies reported diarrhea and nausea and vomiting. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 0 - 4%, all doses = 3 - 8%), 2) dizziness (placebo = 3%, all doses = 0 - 8%), 3) diarrhea (placebo = 3%, all doses = 2 - 33%), 4) agitation (placebo = 4%, all doses = 1 - 4%), and 5) eating disorder (placebo = 1%, all doses 2 - 4%).

Various cholinergic neurotransmitter modifying agents. See Evidence Tables 83 through 93 at http://www.ahrq.gov/clinic/epcindex.htm. See Summary Table 11.

The remaining agents classified as cholinergic neurotransmitter modifying agents were grouped according to the number of studies for the purposes of presentation:

Cholinergic pharmacological agents that had two trials eligible for this review and were compared to placebo.

Eptastigmine (Evidence Tables 83, 84, 85, 93). Two trials[118,119] evaluated eptastigmine in patients with mild to moderate AD (103 patients for 4 weeks and in 491 patients for 24 weeks). Both trials were industry-funded. The trial that used an ITT analysis[118] and had the longer duration (24 weeks) showed significant change in the three domains: general cognitive function, global assessment, and quality of life/ADL. The OC analysis[119] of the patients treated for 4 weeks showed no significant effect. One trial used the ADAS-cog as a primary outcome[118] and showed a small increase of 1.05 and 0.41 for the 15 and 20 mg thrice daily doses, respectively, relative to the placebo group (which increased by 2.6 points). The CIBIC+ was significant for the higher dose group only in this same trial. The evidence of benefit for eptastigmine remains inconclusive given the lack of consistency between studies.

Linopirdine (Evidence Tables 83, 87, 88, 93). Two 1997 trials[120,121] evaluated linopirdine in patients with mild to moderate AD patients for 4 or 6 weeks at 40 or 30 mg thrice daily. Both were at least partially industry-funded. One trial[120] included 382 patients on 30 mg dose during a 6 month trial and used an ITT analysis; this study showed statistically significant findings for general cognitive function alone as measured with the ADAS-cog (mean change 2.0 points); global assessment, quality of life/ADL, and behavior/mood were not significant. All outcomes evaluated in the second trial[121] were not significant, even though OC analysis was used.

Cholinergic pharmacological agents with only one trial eligible for this systematic review.

Huperzine-A (Evidence Tables 83, 92, 93). This study[122] showed a statistically significant benefit relative to placebo in an OC analysis of all domains that were evaluated: general cognitive function, behavior/mood, and quality of life/ADL. The study population was 103 Asian patients with mild to moderate AD, who were treated for 8 weeks.

Sabeluzole (Evidence Tables 83, 89, 93). This study[123] included 39 patients with mild to moderate AD and lasted 48 weeks. General cognitive function as measured by the ADAS-cog showed approximately a 5 point increase compared to a 7 point increase for placebo. The OC analysis showed no significant difference from placebo in general cognition.

Results of non-cholinergic neurotransmitter/neuropeptide modifying agents (NCNMA)

A total of 35 drugs in 50 studies were classified as non-cholinergic neurotransmitter/neuropeptide modifying agents. These pharmacological agents can be seen in Table 3. Sixteen of these studies involved direct comparisons to other drugs and these are considered separately in the section addressing Question Three. Overall results for each of the trials each intervention are detailed in OST located at the end of this chapter and organized by drug. All other study details are available in Evidence Tables 95 through 161 in the Appendices.

Table 3. List of Non-cholinergic neurotransmitter/neuropeptide modifying agents and the number of studies vs. placebo for each of these. Asterisk (*) indicates report of a drug vs. drug trial [comparator drug(s) in brackets].

Drug	Number of studies vs. placebo	Drug	Number of studies vs. placebo
Alaproclate	1	Memantine	3
Alprazolam *[Lorazepam]	0*	Mianserin *[Citalopram]	0*
Anapsos	1	Minaprine	1
BMY (Nootropic)	1	Moclobemide	1
Carbamazepine	2	Naftidrofuryl	1
Citalopram *[Mianserin] *[Perphenazine]	2**	Olanzapine *[Lorazepam]	2*
Diphenhydramine *[Haloperidol, Oxazepam]	0*	Oxazepam *[Diphenhydramine Haloperidol]	0*
Divalproex	2	Paroxetine *[Imipramine]	0*
Fluoxetine *[Haloperidol] *[Amitriptyline]	2**	Perphenazine *[Citalopram]	1*
Fluvoxamine	1	Phosphatidylserine	2
Haloperidol **[Risperidone] *[Loxapine] *[Diphenhydramine Oxazepam] *[Fluoxetine] *[Tiapride] *[Trazodone]	4*******	Risperidone **[Haloperidol]	1**

Table 3. List of Non-cholinergic neurotransmitter/neuropeptide modifying agents and the number of studies vs. placebo for each of these. Asterisk (*) indicates report of a drug vs. drug trial [comparator drug(s) in brackets] (continued).

Drug	Number of studies vs. placebo	Drug	Number of studies vs. placebo
Imipramine *[Paroxetine]	1*	Selegiline *[Vitamin E]	7*
Lisuride	1	Sertraline	2
Lorazepam *[Alprazolam] *[Olanzapine]	1**	Thioridazine *[Loxapine]	1*
Loxapine *[Haloperidol] *[Thioridazine]	1**	Tiapride *[Haloperidol] *[Melperone]	1**
Lu25-109	1	Trazodone *[Haloperidol] *[5'-MTHF]	1**
Maprotiline	1	Xanomeline	1
Melperone *[Tiapride]	0*		

Haloperidol. See Evidence Tables 94 through 103 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Five studies[124,125,126,127,128] evaluating haloperidol relative to placebo as well as another drug were included in this review. Three additional trials[129,130,131] (from 1990, 1993, and 2001) compared haloperidol to another drug and did not include a placebo group (these are detailed in question 3). One study was published in each of 1982, 1997, and 1999; two were from 2000.

Design/methodology. Sample sizes for the placebo-controlled studies were generally small with samples of 15,[128] 64,[126] 149,[125] 344,[127] and 306[124] for an overall total sample size of 622 subjects. All but one of the studies had a quality score of 6 out of a possible 8 points; the other study[127] had a score of 7 points. One study[124] did not indicate a funding source, three studies[125,126,127] indicated some industry funding, although none showed total industry funding, and one study[128] had no industry funding.

Populations. Populations evaluated in the studies included three with only mild to moderate or probable AD,[124,125,128] one with PDD and MID,[126] and one with PDD, VaD, and mixed dementia[127] (which reported subgroup information about VaD versus all subjects). Two placebo studies[126] reported the presence of subjects with severe disease. Two trials[126,127] studied institutionalized patients while one[128] looked at community subjects. Ages in the studies ranged from a mean of 72.7 to 81.0 years, and 33 - 49% of subjects were male.

Intervention. Haloperidol doses ranged from 3 mg to 20 mg per day for a treatment period of 3 weeks,[124] 6 weeks,[128] 10 weeks,[126] 12 weeks[127] or 16 weeks.[125] The other drugs that haloperidol was compared to included fluoxetine,[128] loxapine,[126] risperidone,[127] tiapride,[124] trazodone & BMT[125] in the placebo controlled studies; loxapine,[129] risperidone,[131] oxazepam & diphenhydramine[130] were evaluated in the head to head comparisons.

Primary outcomes. All studies evaluated behavioral outcomes, and at least one study evaluated the effect of haloperidol in each of the other domains included in this review with the exception of specific cognitive function. None of the studies reported baseline MMSE values.

Analysis. Two studies[124,127] reported ITT analysis and three[128,126,125] did not.

Results and interpretation. See Summary Table 12. Of the five studies that had a placebo group, only three trials evaluated general cognitive function. One trial[127] did not report the results for this domain and two showed no significant difference.[124,125] Three trials[124,126,127] found statistical differences for outcomes in the behavior/mood domain, and two trials[128,125] showed no change. One of these non-significant trials[128] evaluating behavior had a very small sample size (n = 12) and was likely underpowered. Four trials evaluated global function, and the two studies[124,125] that reported findings based on the CGIC and CGI showed both improvement and no benefit, suggesting inconsistent evidence for this domain; it should be noted that one of these trials lasted for only 3 weeks.[124] One trial evaluated quality of life using the IADL and showed statistical difference in favor of the placebo. Two trials[125,128] evaluated caregiver burden and showed no effect; one of these studies[128] had very small sample size and was likely underpowered. There were not enough similar outcomes reported to complete a pooled analysis for haloperidol.

The quality scores for reporting adverse events varied from 1 to 5. Only three of five studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 5 – 17% for placebo and 17 – 33% in the treatment group. One trial[124] showed a dose response effect, but the study only lasted for 3 weeks. Three trials tested for differences between treatment and placebo with respect to extrapyramidal symptoms (placebo = 17 - 32%, all doses = 34 - 97%), and two[124,125] found significant differences. One study[125] found significant differences between groups for balance-related problems. Although reported by only two trials, the range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = not reported), and 2) dizziness (placebo = 24%, all doses = 21%), 3) no frequencies were reported for agitation, diarrhea, or eating disorder.

Memantine. See Evidence Tables 104 through 108 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Three studies comparing memantine to placebo were eligible for review. One study was published in 1999[132] and the other two[133,134] in 2002.

Design/methodology. Sample sizes ranged from 166 to 579 for a total population evaluated of 1066 subjects. Two studies[132,133] earned 6 points out of 8 for the quality score while the other[134] earned 7 points. One report[132] did not indicate the source of funding, and the other two had industry support or funding.

Populations. Two studies[133,134] included VaD patients only, one of which[134] analyzed subgroups based on MMSE, type of VaD, and gender. The other study[132] included VaD, DAT and PDD patients and did subgroup analysis comparing VaD to DAT and grouping for care dependence. One trial[132] included patients with severe disease and was the only study to report that all of their subjects were institutionalized. One study[134] included only community subjects and the other study[133] did not report source of patients. Study subjects had a mean age of 71.2,[132] 76.4,[133] and 77.4[134] years, and 42 - 53% were male.

Intervention. Two studies[133,134] had a 4 week titration period with a final dose of 20 mg per day for the remaining 24 week study duration. The third study used a 2-week titration period with a final dose of 10 mg per day for the remaining 10 weeks of the study.

Primary outcomes. All studies evaluated global function. The ADAS-cog was evaluated in two studies[134,133] and showed smaller changes of decline relative to placebo by approximately 1.5 points. All studies measured global function with the CGI-C but did not provide variance data to permit the calculation of the pooled estimates. Although, all trials measured MMSE, none reported baseline values for this outcome. Only one trial[132] evaluated behavior/mood and quality of life/ADL. No study evaluated specific cognitive function or caregiver burden.

Analysis. All studies performed ITT analysis.

Results and interpretation. See Summary Table 13. Two studies[134,133] in subjects with mild to moderate VaD showed significant findings for general cognitive function but not global assessment. The power could be estimated for one of these trials[133] and was found to be below acceptable levels (PW= 0.60). The third memantine trial[132] in this review evaluated mixed dementia populations (including some VaD) with moderate to severe dementia and found significant differences for global function, behavior/mood, and quality of life/ADL, but did not evaluate general cognitive function. It should be noted that this trial[132] used half the dose of memantine for half the study duration in patients with greater disease severity, and had approximately half the sample size of the other two trials evaluated in this systematic review. There were not enough similar outcomes reported to complete a pooled analysis for Memantine.

The quality scores for reporting adverse events varied from 3 to 4. Only two of three studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 7 – 13% for placebo and 9 – 12% in the treatment group. One trial[133] tested for differences between treatment and placebo, and none of the comparisons were significant. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all does = 5%), 2) dizziness (placebo = 3 - 8%, all doses = 6 - 11%), 3) diarrhea (placebo = 4%, all doses = 4%), 4) agitation (placebo = 7 - 8%, all doses = 4 - 5%), and none reported eating disorder as an adverse event.

Selegiline. See Evidence Tables 109 through 116 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Six studies evaluated the effect of selegiline compared to placebo.[135,136,137,138,139,140] A single study[135] compared selegiline to vitamin E, placebo and the combination of selegiline plus vitamin E . The studies were published in 1991,[136] 1992,[137] 1993,[138] 1997,[135] 1998,[140] and 1999.[139]

Design/methodology. Sample sizes ranged from 10[137] to 341[135] with a total population evaluated of 733 subjects. Study quality scores were 5,[140,135,137] 6,[139,138] and 7.[136] Three trials[139,137,136] did not report the source of funding, and the other three[140,135,138] had some industry support.

Populations. Studies included patients with mild to moderate PDD, DAT, and AD. Two subgroup analyses based on the results of the clock drawing test[139] and the GDS result[136] were

reported. One study reported that the included patients were institutionalized.[139] Mean age of the subjects in the trials ranged from 68.6 to 83.0 years and all had male subjects (29 – 74%).

Intervention. All trials used the same dose, 10 mg per day, with three of the trials[135,138,137] giving the drug in two 5 mg doses. One trial[140] reported a titration period of 7 days. The duration of the trials varied with treatment times of 2 months,[137] 3 months,[136] 6 months,[139,140] 15 months,[138] and 24 months.[135]

Primary outcomes. Quality of life/ADL and caregiver burden were not evaluated in any of the studies.

Analysis. Two studies[135,140] carried out ITT analysis.

Results and interpretation. See Summary Table 14. Five of the six trials evaluated general cognitive function, and of these, only four reported their findings. Two of the trials[138,140] showed non-significant findings, but these had very small sample sizes (10 and 41 subjects) and were likely underpowered. Two trials[137,139] showed mixed results, and one of these was likely underpowered.[137] One trial[136] found significant changes for specific cognitive tests (Sternberg Memory tests). Similarly, this same trial showed significant differences for global assessment and behavior/mood. This is the only trial that showed consistently positive findings across domains tested, and it also had the highest quality score (7). However, the other studies evaluating specific cognitive functions, global assessment, and behavior/mood did not show consistent results (non-significant or mixed findings). There were not enough similar outcomes reported to complete a pooled analysis for selegiline.

There is some evidence that shows that selegiline and selegiline combined with vitamin E, increases the time to important functional decline milestones[135] using time to event in the survival analysis. The results of this study showed that the vitamin E, selegiline, and combined groups were statistically different (i.e., declined less) from the placebo group in analyses that included baseline MMSE score as a covariate (not significant when excluded). The median survival was 230 days (vitamin E), 215 days (selegiline), and 145 days (combined group). Moreover, the vitamin E group showed a statistically significant difference for the endpoint of institutionalization, and the other treatment groups did not. Thus, the findings of this study suggest that selegiline and vitamin E may delay clinically important deterioration in patients with moderately severe AD; this delay varied from 20 to 32 weeks. It should be noted that this study evaluated subjects over a 2 year period, the longest of any dementia trial; moreover, the population was moderate to severe with respect to severity.

The quality scores for reporting adverse events varied from 0 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0 - 4% for placebo and 0 – 9% in the treatment group. Two trials[137,138] did not report any adverse events. Only one trial[135] tested for differences between the treatment and placebo groups and showed that balance (worse) and falls were significantly different between groups (particularly the group with selegiline combined with vitamin E (22%) versus placebo (5%)). However, when adjusted for multiple comparisons, these were no longer significant. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 2%, all doses = 0%), 2) dizziness (placebo = 2 - 20%, all

doses = 0 - 30%), and 3) agitation (placebo = 4 - 16%, all doses = 4 - 23%); no trial diarrhea or reported eating disorder as an adverse event.

Various non-cholinergic neurotransmitter/neuropeptide modifying agents. See Evidence Tables 117 through 160 at http://www.ahrq.gov/clinic/epcindex.htm. See Summary Table 15.

Ten non-cholinergic neurotransmitter neuropeptide modifying agents versus placebo were studied in only two included trials:

Anapsos (Evidence Tables 117, 119, 120, 160). Anapsos versus placebo was reported for a total of 114 patients with AD or VaD in reports published 1993[141] and 2000.[142] Both studies were partially funded by industry, and varied in the drug dose and duration; one trial[142] used 360 mg per day or 720 mg per day for 4 weeks, and the other trial[141] used 300 mg three times a day for 12 weeks. They each reported only one domain, and showed a significant change for general cognitive function[142] and no significant results for global assessment.[141]

Carbamazepine (Evidence Tables 117, 121, 122, 160). Two trials [143,144] evaluated carbamazepine in a total of 72 patients. The 1998 study[144] included a mixed severity population of institutionalized patients with non-industry–funding but also some financial support from industry. Both studies titrated up from 100 mg per day to 300 mg per day for 6 weeks. They evaluated all domains except caregiver burden. The trial using OC[143] population showed no significant effect for all outcomes tested but was likely underpowered (n = 16). The trial using ITT[144] showed a significant change in global assessment and behavior/mood. The evidence for benefit remains inconclusive given the lack of consistency between trials.

Citalopram (Evidence Tables 117, 123, 124, 160). Citalopram was evaluated in a total of 183 patients with mixed dementias including AD, VaD, mixed, MID, PDD. One trial[145] was non-industry–funded and the other[146] did not report funding source. Treatment was 20 mg per day for two weeks in both trials, with one continuing for 2 more weeks with 30 mg per day. One trial[146] measured the global effect and had mixed results. Both studies measured behavior/mood: one[145] showing significant change and the other[146] showing no significant change.

Divalproex sodium (Evidence Tables 117, 125, 126, 160). Divalproex sodium was evaluated in 229 subjects with mixed populations of VaD and AD who were treated for 6 weeks with increasing dosages until 20 mg per kg daily[147] or until side effects appeared.[148] These trials were both industry-supported or funded and included 56 or 173 institutionalized patients with probable or possible disease. Both trials showed no significant change in cognition and behavior/mood, while only one study[148] measured quality of life/ADL and found no significant difference. Both trials did a global assessment; one study found no significant difference,[148] and the other[147] found a significant change in favor of placebo.

Fluoxetine (Evidence Tables 117, 140, 141, 160). Fluoxetine was studied in a total of 56 AD patients using 3 or 20 mg per day[128] or a titration from 10 to 40 mg per day[149] for 6 weeks. All patients included in one study[149] also had major or minor depression. One study[128] was not industry-funded, and the other[149] did not indicate the funding source. Overall, the two studies

evaluated general cognition, behavior/mood, quality of life/ADL, and caregiver burden; no significant differences between the drug and placebo were found.

Loxapine (Evidence Tables 117, 147, 159, 160). Loxapine was evaluated in two trials[150,126] from 1982 and included a total of 124 patients with MID and PDD. One trial[126] reported moderate to severe disease. The mean age in the other trial[150] was 83.0 years compared to 72.7 years in the trial with severe patients. Both studies were partially funded by industry and lasted 8 or 10 weeks. Only two domains were evaluated: global assessment and behavior /mood. No significant difference was shown in one trial,[150] while the other trial[126] showed a significant difference for behavior/mood.

Olanzapine (Evidence Tables 117, 135, 146, 160). Olanzapine was evaluated by two industry-funded trials in a total of 478 institutionalized patients with AD, VaD, and mixed dementia. One study[151] used 10 or 15 mg per day for 6 weeks and the other[152] used 12.5 mg maximum for one day. Both studies showed no significant change in general cognition. Both showed a significant change in measures of behavior/mood. One study[152] evaluated global assessment and found no significant differences.

Phosphatidylserine (Evidence Tables 117, 136, 137, 160). Two industry-funded trials studied a total of 193 patients with AD or PDD. One study[153] included institutionalized patients with mild to severe AD and a mean age of 62.1 years, and the other[154] included community patients with mild to moderate AD or PDD and a mean age of 71.0 years. Both studies did subgroup analysis based on severity of illness. The study of institutionalized patients[153] found significant change in the domain of general cognition and global assessment. The study with community patients found significant change in a global assessment but no significant change in a measure of quality of life/ADL.

Risperidone (Evidence Tables 117, 142, 144, 160). Two studies evaluated risperidone for 12 weeks in 625 AD, VaD, or mixed dementia patients with moderate to severe disease[155] and in 344 PDD, VaD, or mixed dementia patients with severe disease.[127] The studies were industry-funded or supported, and both did subgroup analysis: one by disease and the other by gender, age, race, and diagnosis. Both trials showed a significant change in a global assessment. One study[155] found a significant change in behavior/mood, and the other study[127] had mixed results for that domain. There was no significant change in cognition or quality of life/ADL according to one of the trials.[127]

Sertraline (Evidence Tables 117, 138, 139, 160). Sertraline was evaluated in two studies: one trial[156] for 8 weeks in 31 late-stage institutionalized AD patients with major depression (mean age 89.0 years), and the other trial[157] for 13 weeks in a community sample of 22 patients with mild to moderate AD and depression (mean age 77.0 years). Both studies found no significant differences in cognition. The trial[156] in subjects with severe disease found no significant difference in behavior/mood; the second trial[157] had mixed results for this same domain. The study in patients with mild to moderate disease showed significant change for a global assessment and no significance for quality of life/ADL.

Non-cholinergic neurotransmitter/neuropeptide modifying interventions (NCNMA). Fifteen drugs in this drug grouping were compared to placebo in only one included trial. Eight of these trials showed a significant difference from placebo (See Evidence Tables 117, 120, 128, 129, 133, 134, 143, 145, 149, 160 at http://www.ahrq.gov/clinic/epcindex.htm): Alaproclate[158] for 4 weeks in 43 institutionalized patients with mild to severe PDD, MID and mixed dementia was better for quality of life/ADL. Imipramine[159] for 8 weeks in a community sample of 61 PDD and AD patients with depression was better for global assessment. Lisuride[160] for 8 weeks in 22 patients with mild to moderately severe AD was better for cognition. Minaprine[161] for 12 weeks in an institutionalized sample of MID or SDAT patients showed mixed results for behavior. Moclobemide[162] for 6 weeks in 511 patients with mild to moderate AD who were from both the community and institutions was better for cognition and behavior/mood. Naftidrofuryl[163] for 6 months in 378 patients with mild to severe VaD or mixed dementia was better for cognition and global assessment. Tiapride[124] for 3 weeks in 306 institutionalized AD patients with aggressiveness or irritability was better for behavior/mood. Trazodone[125] for 16 weeks in 149 AD patients from the community was better for quality of life/ADL. Xanomeline[164] in 343 community AD patients for 6 months was better for cognition, global assessment, and quality of life/ADL.

Seven trials (See Evidence Tables 119, 127, 130, 131, 132, 146, 147, 148, 160 at http://www.ahrq.gov/clinic/epcindex.htm) found no significant differences from placebo when evaluating perphenazine,[145] thoridazine,[150] fluvoxamine,[165] lorazepam,[152] LU25,[166] maprotiline,[167] and minaprine[161].

Results of other agents

A total of 72 studies representing 46 different other agents were eligible for this review and these can be seen in Table 4. Twenty-two of these interventions were evaluated in a single trial and only briefly summarized in this chapter; greater detail is provided in Evidence Tables 161 through 249.

Table 4. List of Other pharmacological agents and the number of studies vs. placebo for each of these. Asterisk (*) indicates report of a drug vs. drug trial [comparator drug(s) in brackets].

Drug	Number of studies vs. placebo	Drug	Number of studies vs. placebo
Aniracetam	1	Misoprostol *[Diclofenac]	0*
5'-MTHF *[Trazodone]	0*	Monosialotetrahexosylganglioside (GM-1)	1
Amitriptyline *[Fluoxetine]	0*	N-Acetylcysteine	1
Ateroid	1	Nimesulide	1
Buflomedil	1	Nimodipine	2
Cerebrolysin	6	Nizatidine	1
Choro-San	1	Nootropic	1
Choto-San	1	ORG 2766	2

Table 4. List of Other pharmacological agents and the number of studies vs. placebo for each of these. Asterisk (*) indicates report of a drug vs. drug trial [comparator drug(s) in brackets] (continued).

Drug	Number of studies vs. placebo	Drug	Number of studies vs. placebo
Citicoline *[Posatirelin] *[Sulphomucopolysaccharides]	0**	Oxiracetam	5
Cyclandelate	2	Pentoxifylline *[Sulodexide]	3*
Denbufylline	1	Piracetam	1
Desferrioxamine	1	Prednisone	1
Diclofenac	1	Propentofylline	4
Ergokryptine (CMB 36-733)	1	Pyritinol *[Hydergine]	0*
Ergokryptine (Dek)	1	Silymarin + Tacrine *[Placebo + Tacrine]	0*
Estrogens	5	Simvastatin	1
Ginkgo Biloba	3	Sulphomucopolysaccharides *[Citicoline]	0*
Glycosaminoglycan Polysulfate	1	Sulodexide *[Pentoxifylline]	0*
Guanfacine	1	Thiamine	1
Hydergine *[Pyritinol]	1*	Vasopressin (DDAVP)	1
Hydroxychloroquine	1	Vincamine	1
Idebenone *[Tacrine]	4*	Vitamin E *[Donepezil] *[Selegiline]	1**
Indomethacin	1	Xantinolnicotinate	1

Cerebrolysin. See Evidence Tables 161 through 168 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Six included studies [168,169,170,171,172,173] compared cerebrolysin to placebo. One report was from 1994,[172] one from 1999,[171] two from 2000,[169,170] one from 2001,[168] and one from 2002.[173]

Design/methodology. The sample size in the studies ranged from 53[169] to 192[173] with a total of 819 subjects. The quality of studies varied from scoring 6[171] to 8[168,173] points out of a possible 8 points. One study[172] did not indicate the source of funding, one trial had non-industry funding,[173] and the four remaining trials were funded by industry.[168,169,170,171]

Populations. All but one of the six studies included AD patients; one study[171] evaluated patients who had mild to moderate VaD. Mean ages of the subjects in the studies ranged from 69.7[171] to 74.1 years.[173] The proportion of males in the trials varied from 34 - 69%, and only one trial[173] specified the proportion of Caucasians.

Intervention. All of the studies used the same dose of cerebrolysin, 30 ml per day, for 5 days per week. One trial[172] was for 28 days, four studies[169,170,171] lasted 4 weeks, one trial[168] lasted 16 weeks, and one trial[173]lasted 24 weeks.

Primary outcomes. Most studies evaluated general cognitive function and three trials[168,169,173] used the ADAS-cog. Baseline MMSE was reported in a single trial[173] with a score of 21. All studies evaluated global function, and at least two studies evaluated one outcome in each of the remaining domains with the exception of caregiver burden.

Analysis. All but one[173] of the studies used ITT analysis.

Results and interpretation. See Summary Table 16. Four of the five studies that evaluated general cognitive function showed significant differences.[169,168,170,171] Figure 19 displays the pooled estimate for those studies for which the appropriate data could be extracted for the ADAS-cog. Although a summary estimate was calculated, the test for heterogeneity was positive, suggesting the estimate should be interpreted with caution. Moreover, the overall estimate was not significant. One study[173] showed no significant difference in MMSE or ADAS-cog. This was the only study to report non-industry funding and coincidentally the only study to use OC population analysis. Three studies used specific cognitive measures, two of which[172,171] found significant differences and one of which[170] showed mixed results.

All trials evaluated global assessment, and all except one trial[171] reported a significant difference. Figure 20 shows the pooled estimate for the CGI. The pooled estimate was calculated, the test for heterogeneity was positive, suggesting the estimate should be interpreted with caution. However, the overall estimate is significant. Three trials reported results for a measure of behavior/mood, one showing significant effects[168] and the other two[171] showing none. All trials carried out evaluations of quality of life/ADL measures; one did not report the effect,[168] one had mixed results[170] and the other four showed no significant difference.[169,173,172,171] No study measured caregiver burden.

Figure 19. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing cerebrolysin versus placebo.

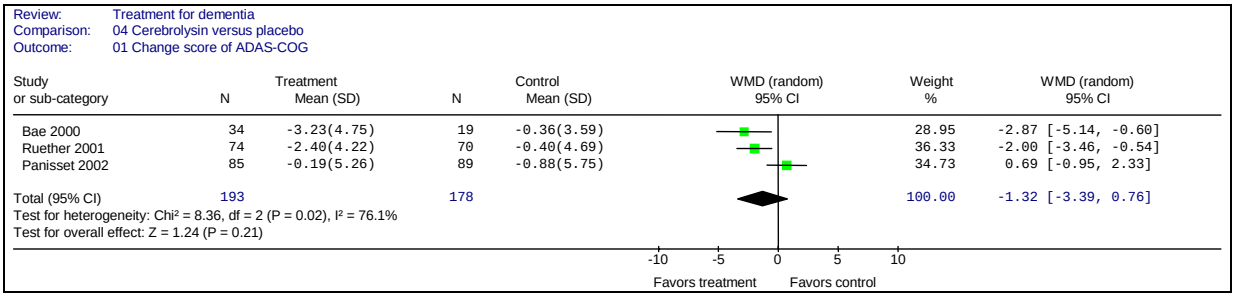
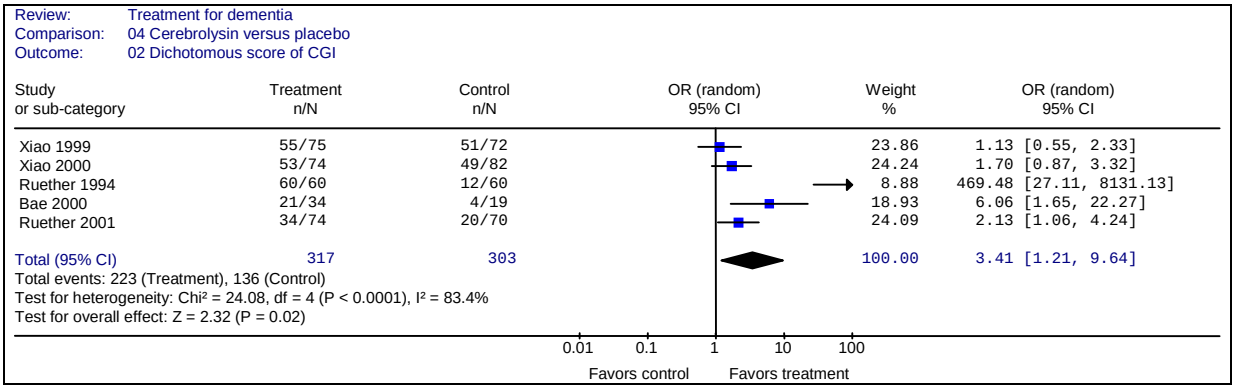


Figure 20. Odd Ratio (OR) from the Random Effects Model (Random) for the CGI comparing cerebrolysin versus placebo.



Two[169,172] of the six trials scored 5 out of 5 on our quality scale for rating adverse events, yet they did not report any adverse events. Two studies[173,168] scored 4, and the other two trials scored 3[171] and 2.[170] All the studies with scores equals to 4 or less tested for statistical differences in adverse events between placebo and treatment groups. Withdrawals due to adverse events were not reported in one study,[170] and were 1% in two studies.[173,168] Three studies[169,172,171] reported no withdrawals. A significant difference between treatment and control group was reported in one study[173] for weight change, anxiety, and headache. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 10 - 24%, all doses = 3 - 21%), 2) dizziness (placebo = 0 - 12, all doses = 1 - 8%), and 3) agitation (placebo = 1%, all doses = 0%), and none reported diarrhea or eating disorder as an adverse event.

Estrogens. See Evidence Tables 169 through 175 at http://www.ahrq.gov/clinic/epcindex.htm.
Number of studies. Five studies[174,175,176,177,178] evaluated estrogens for dementia patients: one published in 1999,[178] three in 2000,[176,177,175] and one in 2001.[174] None compared estrogens to another drug.

Design/methodology. The number of subjects included in the studies ranged from 15[178] to 120 subjects[177] with a total of 247 patients. Quality of the studies ranged from 5[174] to 8[178] points out of a possible 8 points. All studies were partially or fully funded by industry.

Populations. Four of the studies[176,177,175,174] included patients with mild to moderate AD, and one study[178] included moderate to severe dementia patients who were all institutionalized. Only one of the studies[178] included male subjects. Mean age ranged from 71.8[175] to 80.0 years[174] in the AD studies, and it was 83.8 in the dementia study.[178]

Intervention. One of the studies with AD patients used 0.10 mg per day[174] for 8 weeks, and the others used 1.25 mg per day for 12 weeks,[175] 16 weeks,[176] and 52 weeks.[177] The study[178] including subjects with severe disease used 2.5 mg per day for 4 weeks.

Primary outcomes. At least one study evaluated each of the included domains with the exception of caregiver burden.

Analysis. Two of the studies[177,175] performed ITT analysis and the other three used OC analysis.

Results and interpretation. See Summary Table 17. Three[176,177,175] trials evaluated general cognitive function and all showed non-significant findings; two trials[176,177] lacked sufficient power (PW = 0.10, PW = 0.44) for the ADAS-cog. Attempts were made to combine the ADAS-cog, but the random-effects model was positive for heterogeneity and the overall effect was not significant. Two trials[174,177] evaluated specific cognitive function, and only one of these, using the Stroop Color Word Interference Test (SCWIT) measure, showed significant differences.[174] Global assessment was undertaken in all trials and found to be not significant in any of these trials. For those trials where power could be estimated,[176,177,175] there was insufficient power for the CGIC, CDR, and CIBIC+ outcomes. For the outcomes of behavior/mood and quality of life/ADL, none of the trials reported significant differences; power for the outcomes used in the trials could not be estimated. Overall, the evidence that estrogen affected general and specific cognitive function, global assessment, behavior/mood, and quality of life/ADL is inconclusive. There were not enough similar outcomes reported to complete a pooled analysis for estrogens.

One[178] of the five trials scored 5 out of 5 on our quality scale for rating adverse events, and surprisingly, this same trial did not report any adverse event. Two trials[176,177] scored 3; one trial[175] scored 2, and one[174] scored 1. This latter study reported adverse events, but did not test for significant differences between groups. Withdrawal rates due to adverse events ranged from 0 - 5% for placebo and 0 -14% for the treatment group. The most frequently reported adverse event was vaginal bleeding,[175,177,176] and a single trial[175] reported a significant difference between placebo and treatment group for vaginal bleeding. It was not clear from the descriptions provided in the study if they had ascertained whether vaginal bleeding was present prior to the trial commencement. Nausea was the single a priori symptom of interest that was reported and by a single trial; frequencies varied from 0% for the placebo group and 4% for the treatment group.

Ginkgo biloba. See Evidence Tables 176 through 180 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Three studies[179,180,181] evaluating Ginkgo biloba were eligible to be included in this review. All of the studies compared the drug to placebo only. One of the studies was reported in 1996[181] and two were reported in 1997.[179,180]

Design/methodology. The studies included evaluated 20 subjects,[180] 216 subjects,[181] and 327 subjects[179] (totaling 563 subjects). Two of the reports[179,181] scored 8 quality points out of a possible 8 points, and the other[180] earned 6 points. One study did not indicate the funding source,[180] and the other two had industry funding.

Populations. All of the studies included a mix of dementia diagnoses as follows: 1) mild to moderately severe AD and MID,[179] 2) mild to moderate DAT and PDD[180], and 3) mild to moderate DAT and MID[181] in community dwelling patients. Two of the studies reported subgroup analysis, one comparing diagnoses and comparing effects based on baseline MMSE score[179] and the other based on diagnosis.[181] The patients in these trials had mean ages of 64.6,[180] 69.0,[179] and 69.6 years.[181]

Intervention. Two of the trials gave 240 mg per day for 3 months[180] and 6 months,[181] and the other trial[179] gave 40 mg three times daily for 12 months.

Primary outcomes. None of the studies reported on quality of life/ADL or caregiver burden.

Analysis. All of the trials used an ITT analysis.

Results and interpretation. See Summary Table 18. Two of the three trials evaluated general cognitive function, and only one of these showed significant results.[179] Two studies[181,180] showed positive results with specific cognitive function. The results for global assessment are inconsistent as only one trial had positive findings,[181] one study had mixed results,[179] and one trial[180] showed non-significant results. This latter study had a very small sample size and lacked sufficient power for some outcomes. Only one trial[181] reported behavior/mood outcomes and found no difference between groups. None of the studies evaluated quality of life/ADL and caregiver burden. There were not enough similar outcomes reported to complete a pooled analysis for ginkgo biloba.

One[180] of the three trials scored 5 out of 5 on our quality scale for rating adverse events. One study[181] scored 4, and one trial[179] scored 3. Two studies[181,180] had no withdrawals due to adverse events, and one trial[179] had a withdrawal rate of 6% for both placebo and treatment groups. Two studies[179,180] did not report any adverse event. One study[181] reported a statistically significant difference between the treatment and the placebo group for skin disorders. The same study reported gastrointestinal and headache adverse effects, but did not test for statistical differences between the placebo and the treatment group. None of the trials reported any of the a priori symptoms of interest.

Idebenone. See Evidence Tables 181 through 187 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Four studies[182,183,184,185] were included in this review that evaluated idebenone versus placebo, and one study[26] compared idebenone to tacrine but not to placebo. The placebo trials were published in 1992,[184] 1994,[182] 1997,[185] and 1998,[183] the tacrine trial was published in 2002 by the same author as a previous placebo trial.[183]

Design/methodology. Sample sizes in the studies ranged from 92[182] to 450 subjects[183] with a total of 950 patients in the placebo-controlled studies. The study comparing idebenone with tacrine included 203 subjects, but a large number withdrew, and only 44 completed the trial. One of the trials[185] earned 5 points out of a possible 8 points on the quality scale, two of the trials earned 6 points,[182,183] and one earned 7 points.[184] None of the placebo studies reported their funding source. The tacrine study earned 7 points on the quality scale and was partially funded by industry.

Populations. The studies included patients with AD, MID, PDD, and DAT. Two of the trials[182,183] reported that the subjects had mild to moderately severe disease and the remainder reported mild to moderate disease. Two of the studies reported subgroup analysis based on disease severity.[185,183] Mean ages in the studies ranged from 69.9[183] to 73.6 years.[184]

Intervention. Dosing schemes were 30 or 90 mg per day for 6 months,[185] 30 mg three times per day for 3 months,[182] 45 mg twice daily for 4 months,[184] and 120 mg three times per day for 12 months.[183] The tacrine trial used 360 mg per day for 14 months.

Primary outcomes. Caregiver burden was the only domain in this review that was not evaluated in at least one of the studies.

Analysis. Two of the studies[183,185] used ITT analysis while the other two used OC analysis. The tacrine trial used ITT analysis.

Results and interpretation. See Summary Table 19. Three trials[183,184,185] found significant differences for general cognitive function. Two trials[185,183] used the ADAS-cog and reported changes that varied from –4.5 to –4.9 for placebo versus –4.4 to –8.8 for the treatment group. The doses varied in these two trials from 90 to 360 mg per day. A single trial[182] evaluated specific cognitive function and showed inconsistent findings. Three trials[182,183,185] evaluated global assessment and all found significant differences relative to placebo. A single trial[185] evaluated behavior/mood and was statistically significant, even though it was a secondary outcome. Two trials[183,184] evaluated quality of life/ADL and were both statistically significant. No study evaluated caregiver burden. These findings suggest some evidence of benefit for general cognitive function, global assessment, and quality of life/ADL. There were not enough similar outcomes reported to complete a pooled analysis for idebenone.

Quality scores for reporting adverse events varied from 1 to 5. Rates of withdrawal due to adverse events varied from 0 - 5% for the placebo group and 0 – 5% in the treatment group; a single trial[183] did not report withdrawal rates. Two trials[183,185] tested for statistical differences between groups and found no differences. Although no clear pattern emerges, three studies identified at least one balance-related adverse event across studies. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 2%, all doses = 2 - 11%), 2) dizziness (placebo = not reported, all doses = 2%), and 3) not reported for diarrhea, agitation, or eating disorder as an adverse event.

Oxiracetam. See Evidence Tables 188 through 194 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Five trials[186,187,188,189,190] included in this review evaluated oxiracetam versus placebo. The studies were published in 1988,[188] 1989,[187] and 1992.[190,189,186]

Design/methodology. A total of 554 patients were included in the studies, ranging from 30 patients[188] to 289 patients.[187] Four of the studies earned 6 points out of a possible 8 points on the quality scale, and the other study[189] earned 4 points. Two of the studies[189,187] did not report the source of their funding, and the other three trials had partial industry funding.

Populations. The trials included a mixture of diagnoses, including AD, PDD, mixed dementia, and MID, and none of the studies reported severe disease. One of the studies[187] performed subgroup analysis based on diagnosis, comparing MID to PDD. The mean age of the subjects included in the trials ranged from 62.0[188] to 73.8 years.[189]

Intervention. All of the trials used a dose of 800 mg twice daily, for a duration of 12[186,187] to 26 weeks.[189]

Primary outcomes. At least one trial evaluating oxiracetam evaluated one of the outcome domains examined in this review with the exception of caregiver burden. A single trial[189] reported baseline MMSE at 22 for both placebo and treatment groups.

Analysis. None of the trials used ITT analysis.

Results and interpretation. See Summary Table 20. Three trials[187,190,189] out of the five studies tested for outcomes on general cognitive function. Only two of these trials[187,190] reported the findings, which were both significant, even though the NMIC and MMSE were used to measure this attribute. Three trials[186,188,190] evaluated specific cognitive function and showed mixed results. A single large trial[187] evaluated global assessment and found significant differences between groups using the Blessed Dementia Scale (Italian version). Three trials[187,188,190] evaluated behavior/mood with the IPSC-E, and of these, a single trial[190] did not show significant differences. One trial[189]reported on Beck Depression Inventory (BDI) but did not show statistical comparisons. Similarly, three trials[186,189,190] evaluated quality of life/ADL, and a single trial[189] showed no significant findings. No study evaluated caregiver burden. There were not enough similar outcomes reported to complete a pooled analysis for oxiracetam.

The quality scores for reporting adverse events varied from 2 to 5. The proportion of withdrawals due to adverse events varied form 0 – 9% for the placebo group and 0 – 6% for the treatment group. No clear pattern for adverse events is evident, but three of the five studies reported gastrointestinal related problems, primarily associated with abdominal pain. Although, only single trials evaluated the range of frequencies of the a priori symptoms of interest are as follows: 1) dizziness (placebo = not reported, all doses = 11%), and 2) agitation (placebo = 1%, all doses = not reported); no trial reported nausea, eating disorder, or diarrhea as an adverse event.

Pentoxifylline. See Evidence Tables 195 through 200 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Three trials[191,192,193] in this review evaluated pentoxifylline versus placebo. One trial,[194] published in 1997, compared pentoxifylline to sulodexide rather than placebo. The placebo trials were published in 1987,[193] 1992,[192] and 1996.[191]

Design/methodology. The studies included 36 patients,[193] 64 patients[192] and 289 patients.[191] The sulodexide trial included 93 patients. All placebo trials had 6 points out of a possible 8 points on the quality scale and had partial or full industry funding. The sulodexide trial earned 5 points on the quality scale and did not report the source of funding.

Populations. The three placebo-controlled trials included patients with mild to moderate MID, and one trial[193] also included PDD patients. The sulodexide trial had only patients with mild to moderate VaD. Subgroup analysis was performed in two trials, looking at MID versus PDD

diagnosis[193] and grouping by vascular change versus discrete stroke.[192] The mean age of the studies ranged from 69.7[191] to 77.0 years.[193]

Intervention. All of the studies gave 1200 mg per day of pentoxifylline; one study gave the drug once a day for 9 months,[191] one study gave 400 mg three times per day for 9 months,[192] and one gave 400 mg three times per day for 3 months.[193] The sulodexide study gave the drug once a day for 6 months.

Primary outcomes. At least one trial evaluated one of the outcome domains examined in this review with the exception of caregiver burden.

Analysis. A single[191] trial used an ITT analysis.

Results and interpretation. See Summary Table 21. All three placebo trials showed non-significant findings for any primary outcome evaluated on all subjects in the study. It should be noted that two of these trials[192,193] had very small sample sizes (n = 38, n =28) that were evaluated in the OC analyses; this suggests that the trials lacked sufficient power to evaluate multiple outcomes. Knezevic et al.[191] had a large sample size (n = 289) and employed an ITT analysis; all primary outcomes evaluated were not significant. The evidence for all outcomes considered in this review are inconclusive for pentoxifylline. There were not enough similar outcomes reported to complete a pooled analysis for pentoxifylline.

The quality scores for reporting adverse events were generally low, varying from 1 to 3. Withdrawal rates due to adverse events varied from 0 – 25% in the placebo group and 0 – 22% in the treatment group. The two studies that reported adverse events indicated the presence of gastrointestinal disturbances, including abdominal pain or nausea and vomiting (placebo = 7% and all doses = 14%). None of the trials reported dizziness, agitation, eating disorder or diarrhea.

Propentofylline. See Evidence Tables 201 through 206 at http://www.ahrq.gov/clinic/epcindex.htm.

Number of studies. Four studies[195,196,197,198] in this review evaluated propentofylline versus placebo. The first trial was published in 1990.[198] Two, by the same author, were published in 1996[196] and 1998.[197] One was published in 1997.[195]

Design/methodology. The number of subjects in the studies ranged from 30 subjects[197,196] to 260 subjects,[195] with a total of 510 subjects. Three of the studies[197,195,196] earned 5 points out of a possible 8 points on the quality scale, and the other study[198] earned 6 points. Only one study indicated the source of funding for the trial,[196] and it was industry-supported.

Populations. The trials included subjects with mild to moderate AD only,[197] VaD only,[196] mild dementia only,[198] and mild to moderate combined AD and VaD.[195] Two trials presented subgroup analysis: one for AD versus VaD,[195] and one based on MMSE baseline score. The mean age in the studies ranged from 64.8 [197] to 72.4 years.[195]

Intervention. All four studies gave 300 mg three times a day for 3 months with the exception of one trial[195] which had a duration of 12 months.

Primary outcomes. At least one trial evaluated one outcome in each of the domains examined in this review with the exception of caregiver burden. Baseline MMSE was reported in two trials[197,198] and varied from 20 and 21 for both placebo and treatment groups.

Analysis. One of the studies[195] used an ITT analysis.

Results and interpretation. See Summary Table 22. All four trials evaluated general cognitive function and the pooled estimate can be seen in Figure 21. Two of the trials[197,196] had small sample sizes and these trials had the widest confidence intervals. The test for heterogeneity did not exceed our threshold of 0.10 for significance; the overall summary effect was significant. Figure 22 shows the pooled estimate for the DSST, a measure of specific cognitive function; this pooled estimate should be interpreted with caution as the test for heterogeneity was significant and the overall effect was not significant. Thus, there is some evidence of benefit for general cognitive function, and inconclusive evidence for specific cognitive function as measured by the DSST. Similarly, there is inconclusive evidence for global assessment. Behavior/mood outcomes (using the NAB) were evaluated by a single trial[195] and shown to be significantly different; this same trial evaluated quality of life/ADL (using the NAA) and showed no significant difference.

The quality scores for reporting adverse events varied from 1 to 4. The percentage of withdrawals varied from 0 – 13% for the placebo group and 0 – 12% for the treatment group. None of the trials tested for differences between groups. Three of the trials[195,197,198] reported gastrointestinal events that included abdominal pain, constipation, and nausea and vomiting (placebo = 2%, all doses = 7%). Dizziness (placebo = 3 - 5%, all doses = 1 - 6%) was the only other a priori symptom of interest.

Figure 21. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the MMSE change score comparing propentofylline versus placebo.

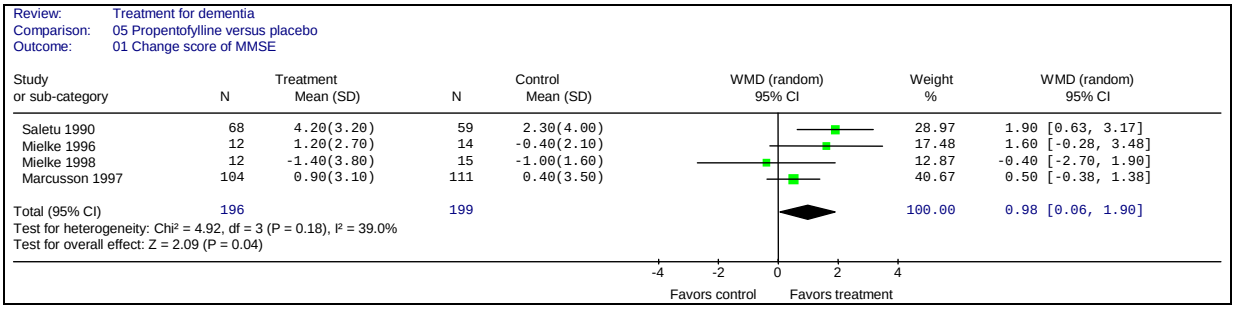
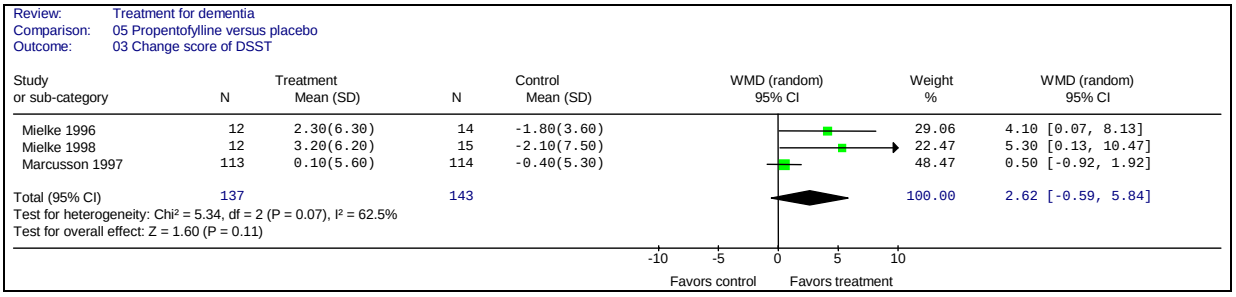


Figure 22. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the DSST change score comparing propentofylline versus placebo.



Various other agents. See Evidence Tables 207 through 249 at http://www.ahrq.gov/clinic/epcindex.htm. See Summary Table 23.

Interventions with two studies included for review. Six other agents were compared with placebo in only two included trials:

Choto-san (Evidence Tables 207, 213, 214, 249) Two studies compared Choto-San with placebo in patients with VaD. Both studies included all Asian subjects and co-morbid disorders were present in both studies. Each study lasted 12 week, with doses of drug at 7.5 g three times a day[199] and 2.5 g three times a day.[200] The studies were published in 1994[200] and 1997[199] and both had a quality score of 5 out of 8 points. Both studies measured global assessment and behavior/mood and disagreed on both results. One study[199] showed a significant change in global assessment and no significant difference in behavior/mood while the other[200] showed mixed results for global assessment and a significant difference for behavior/mood.

Cyclandelate (Evidence Tables 207, 215, 216, 249). Cyclandelate was evaluated in two studies: one[201] in 139 AD patients and another[202] in 196 PDD, VaD, and mixed dementia patients. The mixed population study[202] had a subgroup analysis based on the MMSE, ADAS-cog, and treatment center. The AD patients received 400 mg four times per day for 16 weeks and the mixed population study used 800 mg twice a day for 24 weeks. Only caregiver burden was not evaluated by either study and only global assessment was evaluated by both studies. The study with AD patients[201] showed a significant change in global assessment and in behavior/mood and mixed results in the specific cognitive function measures. The study with the mixed population[202] showed no significant difference in global assessment or general cognitive measures or quality of life/ADL or function.

Ergokryptine (Evidence Tables 207, 212, 218, 249). Two trials, which were not similar, evaluated ergokryptine. One trial[203] that did not indicate the source of funding included 125 PDD patients and treated them with a dose titrated up to 2 mg per day for 8 weeks. The other trial,[204] which was industry funded, treated 215 AD patients with a dose titrated up to 20 mg twice a day for one year. Neither study reported caregiver burden, but both reported general cognitive function and global assessment. They differed on the results of both of those domains: one study[204] showed significant change in cognition and mixed results in global assessment, and the other study[203] showing no significant difference and significant change, respectively. Significant change was demonstrated in specific cognitive measures in the study with AD patients.[204] Mixed

results were shown for behavior/mood outcomes, and no significant difference was seen for quality of life/ADL in the study with PDD patients.[203]

Hydroxychloroquine/Nimesulide (Evidence Tables 207, 226, 229, 249). No significant difference from placebo was seen in either of two studies[205,206] for cognition, behavior/mood, or quality of life/ADL. Global assessment was evaluated in one of the studies[206] and there was no significant difference found. One trial[205] included minimal to mild AD patients and the other[206] included mild to moderate AD patients One study[205] treated patients for 18 months with a dose of 400 or 200 mg per day based on weight. The other study treated for 3 months with 100 mg twice a day. Both studies had non-industry funding, and one study[205] also had industry support.

Nimodipine (Evidence Tables 207, 230, 231, 249). Nimodipine was evaluated in one study[207] with 259 mild to moderate MID patients receiving 30 mg twice a day for 26 weeks. The other study[208] evaluated 178 patients with mild to moderately severe MID and PDD receiving 90 mg per day for 12 weeks. The trials received industry funding or support and were published ten years apart, in 1990[208] and in 2000.[207] The trial using ITT analysis[207] showed no significant difference in the domains of general cognitive function measures, specific cognitive measures, global assessment, and quality of life/ADL. The trial using OC[208] analysis found significant differences in the domains of general cognitive function measures, specific cognitive measures, global assessment, and behavior/mood.

ORG2766 (ACTH peptides) (Evidence Tables 207, 233, 234, 249) Org2766 versus placebo was reported for a total of 233 patients with AD or primary degenerative senile dementia (PDSD) in reports from 1985[209]and 1986.[210,209] One study[209] was industry-supported and used 20 mg twice daily for 6 months, and the other was non-industry–funded[210] and used 80 mg twice daily for 1 month. One study[210] found a statistical difference between drug and placebo in the domains of specific cognitive function measures and in global assessment, and the other study[209] found no significant difference in the domains they evaluated: global assessment and behavior.

Interventions with only one trial included for review. Twenty-two drugs in this drug grouping were compared to placebo in only one included trial. Eleven of these trials showed a significant difference from placebo and are summarized briefly here. See Evidence Tables 207 to 240, 244, 248 and 249 for greater detail concerning the trials.

Drugs compared to placebo in one trial only (Evidence Tables 207, 208, 209, 210, 217, 220, 222, 224, 237, 238, 240, 248, 249) Aniracetam was better for cognition and global assessment in 109 community patients for 6 months, Ateroid[211] in 155 PDD, MID or SDAT patients for 12 weeks was better for general cognition. Desferrioxamine[212] in 48 probable AD patients for 2 years was better for behavior/mood. Glycosaminoglycan polysulfate[213] in 155 moderate to severe PDD or MID patients for 12 weeks was better for behavior/mood. Guanfacine[214] in 29 mild to moderate AD or PDD patients for 13 weeks was better for specific cognitive measures and global assessment. Nootropic agent BMY[215] in 69 mild to moderate AD patients for 12 weeks was better for general cognitive measures. Thiamine[216] in 15 mild to moderate AD patients for 12 months was better for general and specific cognitive function measures. Vincamine[217] for 12 weeks in 152 institutionalized patients with mild to moderate PDD or VaD was better for global assessment. Vitamin E[135] in 341 moderate AD patients for 2 years was better for delaying

institutionalization. Deamino-D-arginine-vasopressin[218] in 14 PDD patients was better for behavior and had mixed results for global assessment. Xantinolnicotinate[219] in 313 mild to moderate AD or MID patients for 12 weeks was better for specific cognitive function measures and global assessment.

Twelve trials (Evidence Tables 207, 211, 219, 221, 223, 225, 227, 228, 232, 235, 236, 239, 244, 249) found no significant differences from placebo or mixed results when evaluating buflomedil,[220] citicoline,[101] denbufylline,[221] diclofenac and misoprostol,[222] hydergine,[223] indomethacin,[224] monosialotetrahexosylgan,[225] N-acetylcysteine,[226] nizatidine,[227] piracetam,[228] prednisone,[229] and simvastatin.[230]

Question 2: Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?

Delay of Onset of Dementia

The concept of "delay onset" was operationalized to imply delay in conversion from a cognitive disturbance state, classified as MCI, CLOND or CIND, to a true dementia state. No studies with this population met the final eligibility criteria, although four trials[231,232,233,234] advanced to the full text screening stage. The lack of studies eligible for evaluation in this systematic review points to a gap in the literature for pharmacological interventions (attempting to demonstrate a delay in disease onset) in MCI-type populations.

Delay of Progression

In general, very few studies evaluated patients who were classified as "severe". Five studies[126,208,129,178,132] had moderate to severe groups of dementia patients, and only one trial reported all three levels[163] of the disease spectrum. The interventions evaluated in these trials were estrogen, haloperidol, glycosaminoglycan polysulfate, memantine, and naftidrofuryl. This suggests that there is a bias in the trials eligible in this systematic review towards evaluating mild to moderate disease; this in turn reflects the underlying assumption that the less severe groups are most likely to benefit from drug trials. Since so few studies have evaluated the more severe groups, this assumption may require some empirical justification. Therefore, delay in progression has not been considered in severe patients.

The selected studies used two approaches for showing "delaying disease progression". The first method for evaluating the potential for a drug to delay disease progression used longer-term follow-up; survival analyses (time to a relevant event) were then used to show differences between the two groups. The second design approach used withdrawal from treatment for a period and continued monitoring of the treatment and placebo groups (to demonstrate a deviation of the treatment group from the natural history as represented by the placebo group). Such designs have been termed withdrawal, active-extension, randomized withdrawal, randomized start, and staggered start.[235,236,19,21] From our 186 included studies, we then further selected a subgroup of papers that had the potential to demonstrate delay in disease progression through the

use of one of these two designs. Therefore, any eligible trial that employed a survival analysis or a two-period approach, where the pharmacological agent was withdrawn during one of the periods, was selected for further evaluation to answer this question.

Survival Analyses

Two studies[135,61] using survival analyses were identified. In a 2-year study[135] that compared placebo to three other groups (selegiline, selegiline with vitamin E, and vitamin E), time to the development of significant dementia milestones (death, institutionalization, loss of ability to perform ADL, or score on scale indicating severe dementia) was used as the time to event in the survival analysis. The results of this study showed that the vitamin E, selegiline, and combined groups were statistically different (i.e. declined less) from the placebo group in analyses that included baseline MMSE score as a covariate (not significant when excluded). The median survival was 230 days (vitamin E), 215 days (selegiline), and 145 days (combined group). Moreover, the vitamin E group showed a statistically significant difference for the endpoint of institutionalization, and the other treatment groups did not. There were no statistical differences between groups with respect to adverse events. Thus, the findings of this study suggest that selegiline and vitamin E may delay clinically important deterioration in patients with moderately severe AD; this delay varied from 20 to 32 weeks. The second study[61] used survival analyses to evaluated the time to the development of severe functional impairments in a comparison of placebo and donepezil with a follow-up of 54 weeks. The results of the Kaplan-Meier analysis showed a mean number of days to significant functional decline of 252 days for placebo and 357 days for the donepezil group (mean difference of 100 days). The treatment group was 38% less likely to decline over a 1-year period. Both these studies demonstrated some delay in disease progress varying from 100 to 230 days for these three different pharmacological agents.

Staggered Withdrawal

Delay in disease progression can also be evaluated using a "time to return to baseline" following withdrawal of treatment. Similarly, staggering the start of the treatment parallels the staggered withdrawal and can be used to evaluate disease progression. In this design approach, the time to return to baseline is compared to the placebo group, which represents the natural course of the disease. Of the studies that were eligible for this research question used a classic withdrawal design (withdrawal in period II after the intervention was administered); none of these studies were able to maintain double blinding after the withdrawal of the intervention. Justification for the selection of the length of the washout or follow-up period was not consistently provided (which possibly reflects the lack of a priori aim to show delay in progression).

Tables 5 and 6 detail any study that attempted to withdraw the drug in the treatment group and then continue observations over time. All studies that reported outcomes after the drug trial endpoint subsequently interrupted protocol and switched to "open-label" circumstances. In open-label conditions, blinding was broken and greater proportions of patients withdrew from the study as the follow-up increased. From a methodological perspective, these data were considered to be biased and would not meet our review eligibility criteria. However, we

summarize in these Tables the same observations that were reported in all the studies eligible for this systematic review.

Table 5. Studies that withdrew the treatment agent but maintained at least single blinding.

Study	Drug	Schedule	Result
Ruether 2001	Cerebrolysin	4w drug + 8w washout + 4w drug + 12w washout	All patients: ADAS-noncog, maintained difference from placebo NAI returned to baseline Subgroup MMSE<20: ADAS Noncog, CGI, ADAS-cog, SKT maintained difference from placebo
Nyth 1990	Citalopram	4w drug + 8 w open drug + 4w new random drug	NR
Rogers 1996	Donepezil	12w drug + 2w SB Pl washout	5 mg maintained effect, 3 mg no maintenance of effect for ADAS-cog (NS)
Rogers 1998b	Donepezil	24w drug + 6w SB and placebo washout	Return to placebo levels for ADAS-cog, MMSE, CIBIC (all NS)
Wilcock 2002	Memantine	2w SB and placebo + 28w drug + 2w SB placebo washout	NR
McKeith 2000	Rivastigmine	20w drug + 3w rest	Return to placebo levels for NPI and computerized cognitive assessment (NS)
Antuono 1995	Velnacrine	2w SB placebo + 24w drug + 6w SB placebo washout	Return to placebo levels for the ADAS-cog but SC for CGIC remained for washout
Bodick 1997	Xanomeline	24w drug + 4 w SB placebo	SC at week 24 with CNTB No differences vs. placebo at w4 of washout

In Table 5, single blinding was maintained in a placebo-controlled trial of cerebrolysin, which had an 8- and 12-week follow-up and showed continuing statistical differences after drug withdrawal. The remaining drug interventions listed in Table 5 suggest that the treatment provided predominately symptomatic relief lasting 2 to 6 weeks and then returning to placebo levels. Similarly, the pharmacological agents in Table 6 suggest that treatment provided only symptomatic relief.

Table 6. Studies that withdrew treatment and did not specify if blinding for washout or extension was maintained.

Study	Drug	Schedule	Result
Dehlin 1985	Alaproclate	2w placebo + 4w drug + 2w placebo	SC for GBS intellectual subscale at w4 of treatment No significant difference at w2 of washout
Cutler 1993	BMY 21,502	12w drug + 4w placebo washout	Treatment showed no significant change and follow-up showed no change
Amaducci 1988	Phosphatidylserine	3m drug + 21 m follow-up	SC remained for severe disease patients, not moderate
Raskind 1997	Metrifonate	26w drug + 8w follow-up	NR
Parnetti 1995	Posatirelin	90d IM + 30d follow-up placebo	“Maintained positive effect” but specific numbers not reported
Agid 1998	Rivastigmine	10w drug + 2w placebo washout	NR

Question 3: Are certain drugs, including alternative medicines (non-pharmaceutical), more effective than others?

From a methodological perspective, addressing the question of being "more effective" requires head to head comparisons of pharmacological interventions. If one intervention (Drug A) has been shown to be effective relative to placebo of a specified effect size, and a second intervention (Drug B) has been shown to be effective at a lower magnitude relative to placebo, it does not necessarily follow that Drug A is more effective than Drug B. Comparisons of the relative effectiveness of certain drugs can only be evaluated in the context of head to head evaluation within the same trial. Those studies undertaken as direct comparisons are summarized below.

Head to Head Comparisons

A total of 26[125,152,129,237,130,238,239,145,150,124,114,131,127,240,241,135,242,101,243,70,194,128,244,26,92,245] studies compared efficacy of two or more pharmacological agents relative to each other. In general, few drugs showed statistically significant differences relative to each other. Those that did include the following (drug performing better is listed first):

1) Sulphomucopolysaccharides versus CDP-choline[238] - Significant differences were seen in favor of sulphomucopolysaccharides in measures of behavior and global assessment in 30 institutionalized patients with mild to moderate MID.
2) Donepezil and vitamin E[70] - Significant differences were seen in favor of donepezil in general cognitive function in 54 patients with mild AD.
3) Antagonic stress versus nicergoline[92] - Significant differences were seen in favor of antagonic stress in cognition as well as a global assessments in 62 subjects with mild to moderate AD.
4) Antagonic stress versus meclofenate[242] - Significant differences were seen in favor of antagonic stress in measures of cognition and global assessment in 63 patients with mild to moderate AD.
5) Posatirelin versus citicoline[101] - Significant differences were seen in favor of posatirelin in general cognitive measure and mood in 222 community living patients with mild to moderate AD.
6) Pyritinol versus hydergine[243] - A significant difference was found in favor of pyritinol in a global assessment measure in 102 Hispanic patients with mild to moderate AD.
7) Idebenone[26] versus tacrine-Mixed results were observed; the Efficacy Index Score showing a significant benefit over tacrine, while the global assessment showed no difference in 203 AD patients, 44 of whom completed the study.

Relative comparisons of FDA approved drugs for the treatment of dementia. Although no head to head trials compared drugs that are likely to be used in current practice in the United States, it was recognized that an assessment of the relative effectiveness of those drugs approved for the treatment of dementia would be of interest to clinicians. Four drug interventions that are currently approved for the treatment of dementia include donepezil, galantamine, rivastigmine,

and tacrine. We caution the reader that inferences drawn from the following figures are limited because these FDA-approved drugs were not compared within the same study. The evidence for benefits and harms has been previously discussed in this report. The pooled estimates (WMD and RR) of two outcomes (ADAS-cog, CIBIC) frequently used in clinical practice have been presented together to illustrate the relative benefit of these approved drugs (Figures 23 to 30). For the purposes of this relative comparison, the pooled estimate reflecting the largest effect size (i.e. the dose showing the greatest magnitude) was selected. Several relevant details should be noted before comparing these estimates as follows: 1) the 5 mg dose of donepezil was selected because the magnitude of the pooled estimate was largest, 2) the 32 mg dose of galantamine had the largest pooled estimate, 3) the rivastigmine pooled estimate for the ADAS-cog was significant for heterogeneity, so the pooled estimate should be considered with great caution, and 4) none of the studies that evaluated tacrine and measured the CIBIC reported sufficient data to estimate an effect size; hence the effect size of the CGIC was substituted for comparison.

Figure 23. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing donepezil versus placebo.

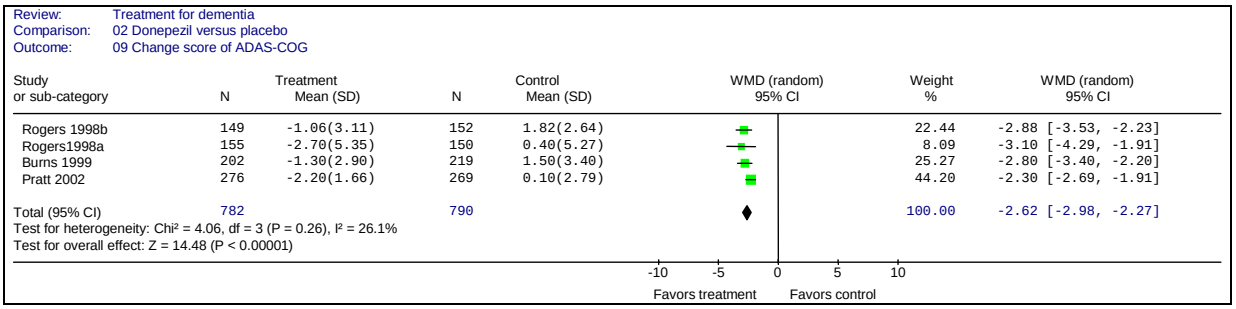


Figure 24. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing galantamine versus placebo.

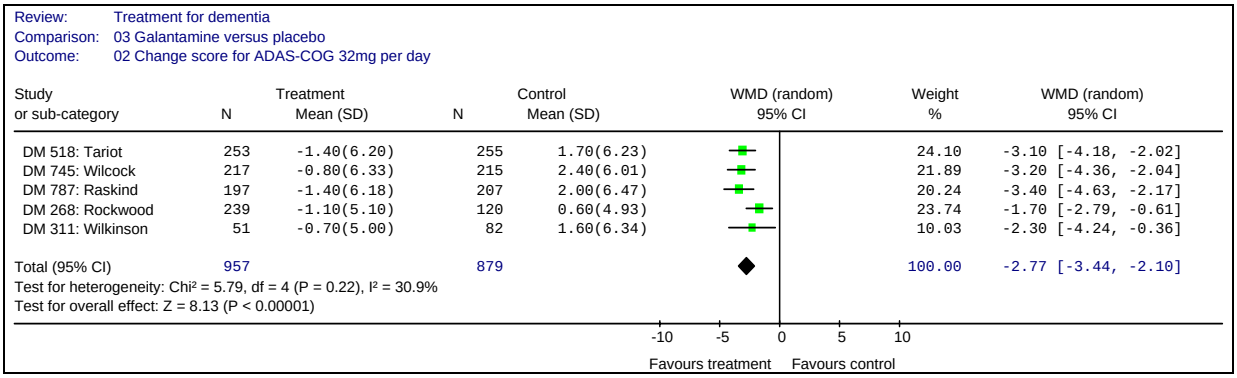


Figure 25. Weighted Mean Difference (WMD) from the Random Effects Model (Random) for the ADAS-cog comparing rivastigmine versus placebo.

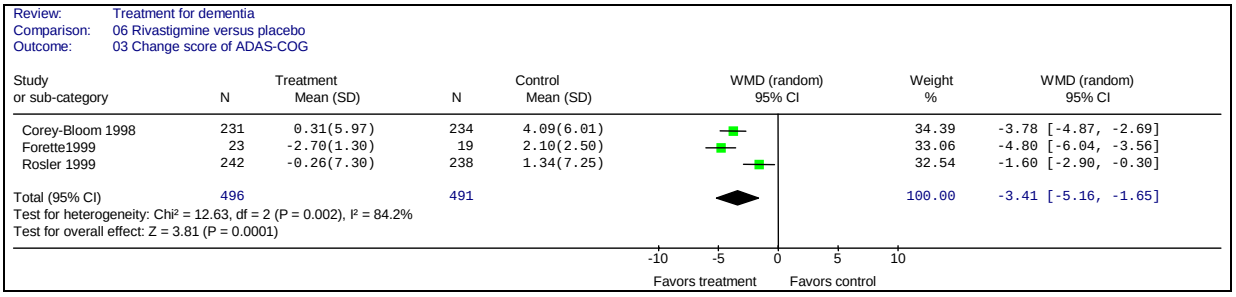


Figure 26. Weighted Mean Difference (WMD) from the Fixed Effects Model (Fixed) for the ADAS-cog comparing tacrine versus placebo.

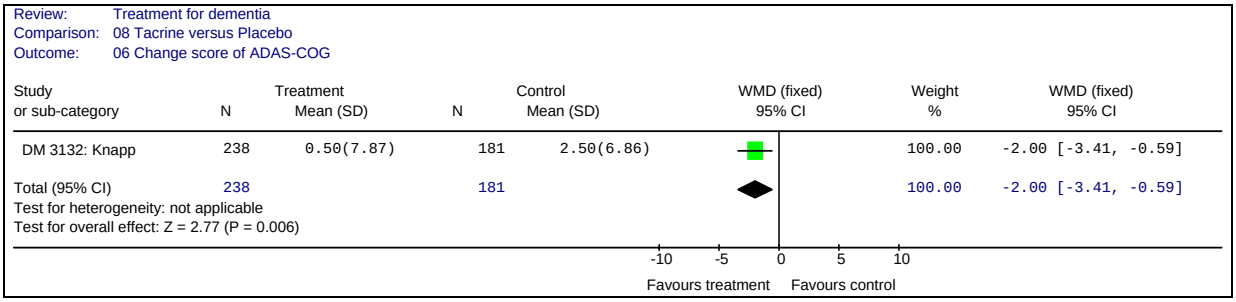


Figure 27. Relative Risk (RR) from the Random Effects Model (Random) for the CIBIC comparing donepezil versus placebo.

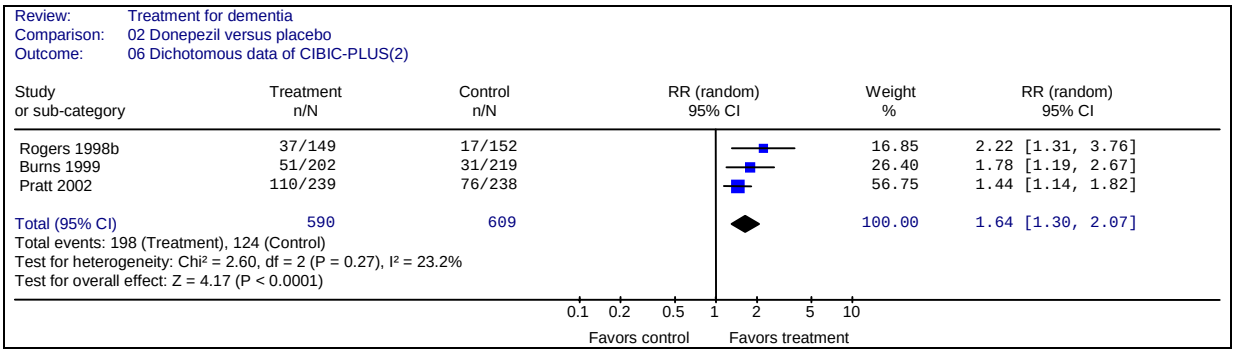


Figure 28. Relative Risk (RR) from the Random Effects Model (Random) for the CIBIC comparing galantamine versus placebo.

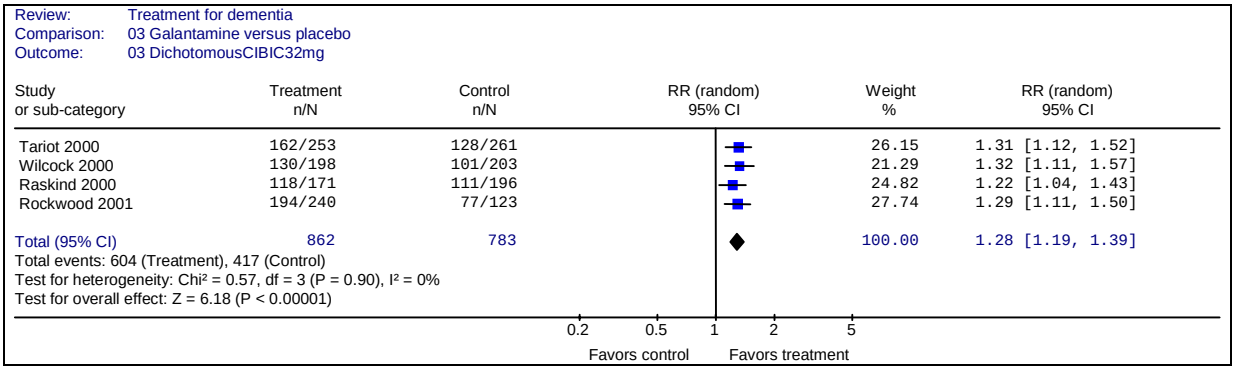


Figure 29. Relative comparison of effect sizes for studies using the CIBIC rivastigmine versus placebo.

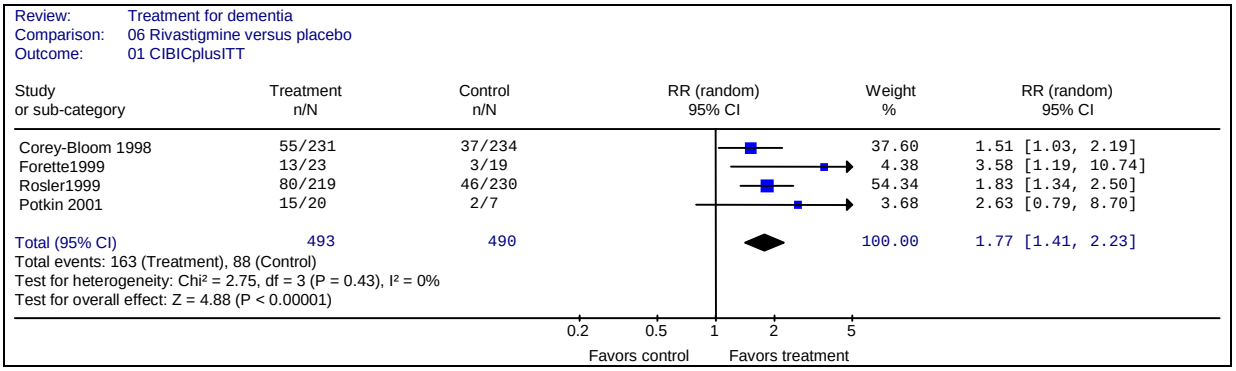
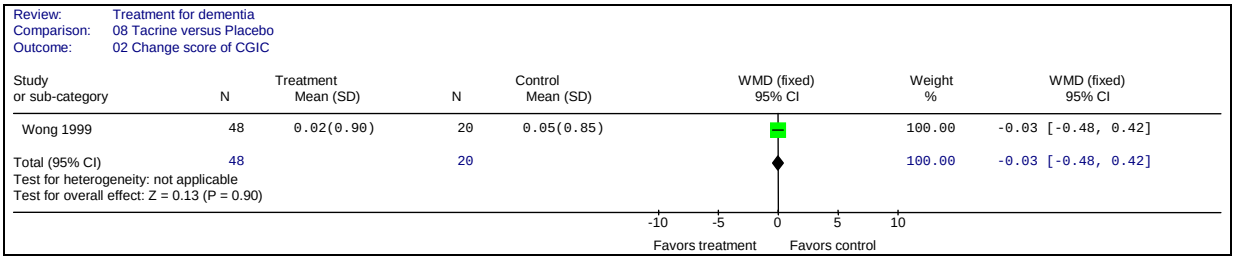


Figure 30. Relative comparison of effect sizes for studies using the CIBIC comparing tacrine versus placebo.



Question 4: Do certain patient populations benefit more from pharmacotherapy than others?

The following studies contained stratified analyses of outcomes for different clinical populations. A total of 22[245,211,146,179,181,132,134,142,183,185,56,168,201,63,64,55,173,62,76,75,60,159] studies addressed this question. During data abstraction, these trials were identified if the methods sections (including analyses) stated that stratified analyses were undertaken. Eight different variables were identified for which stratified analyses were reported. These included: age, gender, APOE genotype, disease type, disease severity (as determined by MMSE/ ADAS-cog

threshold levels), treatment center, care dependence, and presence of depression. Of these 22 studies, seven trials[245,211,146,179,181,132,134] evaluated disease type (AD, PDD, SDAT, MID, VaD). They will be discussed in Question 5 (see below).

Table 7 details the 15[142,26,185,56,246,201,63,64,55,173,62,76,75,60,159] studies that provided stratified analyses other than for disease type. For disease severity, no clear pattern emerges. For APOE, no significant difference was noted between groups[173,62,76,75] for the three interventions that included cerebrolysin, donepezil, and galantamine. For age, Thal et al.[55] conducted a post-hoc analysis to assess the effect of age on the rate of decline. Patients were categorized according to age (< 65 years, 65 years and older). The results of the study indicate that a subgroup of patients, aged 65 years or younger, may benefit more from carnitine as compared to older subjects. Specifically, in the younger population, the significant difference between the treatment and the placebo group was observed for ADAS-cog but not for CDR.

Table 7. Studies with stratified analyses.

CITATION	DRUG	SUBGROUP	DRUG EFFECT
Alvarez 2000	Anapsos	Disease severity	SC in ADAS-cog in patients with mild cognitive deterioration and with AD NS in patients with VD
Gutzmann 1998	Idebenone	Disease severity	NR
Weyer 1997	Idebenone	Disease severity ADAS total score $\geq$ 20	SC for ADAS Total
Sano 1992	Carnitine	MMSE	Low mMMSE group SC on the SRT and CSF levels of drug High mMMSE group NS neuropsychological test scores, CGI ratings and CSF levels of drug
Ruether 2001	Cerebrolysin	MMSE	Subgroup MMSE < 20: SC in CGI, ADAS-cog, NAI and ADAS-Noncog. Suggests it's because this group had reduced placebo response.
Schellenberg 1997	Cyclandelate	MMSE, ADAS-cog, Treatment center	NR
Feldman 2001	Donepezil	MMSE Psychoactive drug use	NR
Tariot 2001a	Donepezil	MMSE (10-26) Age	MMSE group: SC greater differences than for the whole group for MMSE, GDR Older patients group: SC for MMSE, CDR
Thal 1996a	Carnitine	Age	SC age-by-treatment interaction on the ADAS-cog ITT population Patients $\leq$ 65 years significant difference in decline for ADAS-cog favoring Carnitine but not for CDR Patients > 65 years NS
Panisset 2002	Cerebrolysin	APOE genotype	NS association of the APOE e4 status and response to study drug
Winblad 2001b	Donepezil	APOE genotype Gender	NS difference for the subgroups

Table 7. Studies with stratified analyses (continued).

CITATION	DRUG	SUBGROUP	DRUG EFFECT
Raskind 2000	Galantamine	APOE genotype	NS
Wilcock 2000	Galantamine	APOE genotype MMSE	NS for APOE group SC for MMSE < 18
Prasher 2002	Donepezil	Down syndrome ONLY in trial	NR
Reifler 1989	Imipramine	Depression	Depressed patients SC higher HAM-D scale score. For MMSE patients with AD + depression had higher scores initially and improved significantly more over time

SC = Significant change NS = Not statistically significant NR = Not reported

In general, very few studies examined the efficacy of drugs with respect to dementia by population characteristics. Three additional studies attempted to evaluate unique populations or population characteristics. Prasher et al.[60] evaluated subjects who had Down's Syndrome with dementia and were treated with donepezil, and found none of the outcomes to be significant; this study had a sample size of 30 subjects and was underpowered. Ban et al.[213] conducted a multicenter, placebo-controlled, double-blind study with Hispanic and Italian populations. This study was not designed to specifically evaluate the efficacy of glycosaminoglycan polysulfate by ethnicity. However, the study included centers from Mexico, Panama, Naples, and Trieste. This study examined whether the changes encountered in the different outcome measures could be related to center effect, but no statistically significant center effect was found. While this study suggests that ethnicity may have minimal impact, future studies should specifically assess the impact of racial composition on the efficacy of drugs.

Question 5: What is the evidence for the treatment of VaD?

Summary Table 25 details the results of studies in which patients had VaD, or stratified data were presented with respect to VaD subgroups identified as VaD or MID. The trial details for all these studies are provided in evidence tables of key study characteristics, evidence tables of study results, and evidence tables of adverse events found in Appendix C; summary results of trials were also discussed in the results sections of Question 1.

A total of 20 pharmacological interventions in 29 studies[211,220,238,171,200,199,146,68,181,184,133,134,132,161,89,91,93,247,187,191,192,194,193,100,98,196,195,245,217] were applied specifically to dementias classified as VaD. Sixteen studies evaluated populations entirely composed of patients with VaD (or MID), and the remaining 13 trials had VaD as a subgroup. The majority of these pharmacological interventions (n = 14) were represented by a single trial, limiting the extent of the evidence; these included ateroid, buflomedil, cerebrolysin, sulphomucopolysaccharides (CDP choline), citalopram, donepezil, Ginkgo biloba, idebenone, minaprine, nimodipine, nicergoline, oxiracetam, 5-THF (trazodone), vincamine, and xantinolnicotinate. Surprisingly, four of these trials did not report any results relative to placebo,

and these included buflomedil, Ginkgo biloba, oxiracetam, and 5-THF (trazodone); all but one of these trials[220] evaluated subgroups of VaD patients and likely did not posses sufficient power to evaluate differences. Six interventions had more than a single trial, and these included Choto-san (n = 2), memantine (n = 3), nicergoline (n = 2), pentoxifylline (n = 4), posatirelin (n = 2), and propentofylline (n = 2).

Several of the trials with sample sizes greater than 100 subjects showed significant differences in general cognitive function: ateroid, cerebrolysin, donepezil, idebenone, and nicergoline. Similarly, these larger sample studies showed statistical differences for global assessment: Choto-san, donepezil, memantine, nicergoline, propentofylline, vincamine, and xantinolnicotinate. Findings for other outcome domains were inconclusive, as these were rarely evaluated (see Summary Table 25).

Table 8 below lists the studies that undertook comparisons between VaD populations and other dementia types. Although, not consistent across all trials, three of the studies suggests possible differences between 1) MID and AD for 5′-MTHF-trazodone,[245] 2) AD/SDAT and VaD for citalopram,[146] and 3) DAT and MID for Ginkgo biloba.[181]

Table 8. Studies evaluating vascular dementia patients relative to other dementias.

CITATION	DRUG	SUBGROUP	DRUG EFFECT
Passeri 1993	5'-MTHF Trazodone (TRZ)	AD vs. MID	Equivalence study When patients with AD were analyzed separately the same pattern of response to MTHF and TRZ was found in the HDRS and RVM as when they were analyzed together with patients with MID. MID as separate group: HDRS was significantly reduced vs. baseline after 8 weeks of treatment in the TRZ group and only at the end of the follow-up period in the MTHF group. RVM remained unchanged in MID pts in both treatment groups.
Ban 1991b	Ateroid	PDD vs. MID	NR
Nyth 1990	Citalopram	AD/SDAT vs. VaD	A period: No improvement in the VaD group SC in the AD/SDAT group in emotional bluntness, confusion, irritability, anxiety, fear-panic, depressed mood, and restlessness. MADRS scores significantly reduced B period: AD/SDAT group SC in emotional bluntness at week 8. NS at week 4 and 12. NS for the VaD group.
LeBars 1997	Ginkgo biloba	AD vs. MID+AD MMSE	AD subgroup: SC for ADAS-cog and GERRI
Kanowski 1996	Ginkgo biloba	DAT vs. MID	Improvements at 24 weeks of treatment in comparison to baseline values were consistently slightly greater in the DAT group than in the MID group. Calculation of descriptive p-values seemed inappropriate due to the very small number of patients with MID in the sample.
Winblad 1999	Memantine	AD/VaD Care dependence	NR for differences between dementia types Care dependence: Patients with < 20 points on the CGI and BGP Care dependence subscore shows slightly higher response rates than those with >20 points in the memantine group.
Wilcock 2002	Minaprine	SDAT vs. MID	The largest treatment effect occurred in patients with baseline MMSE score < 15 (p = 0.04) and in those without cerebrovascular macro-lesions (p = 0.002)

SC = Significant change NS = Not statistically significant NR = Not reported

Table 9: Guide to Overall Summary Tables – Outcome Measures Classified by Domain

General cognitive function measure	Specific cognitive function measure		Global Assessment	Behavior/Mood	Quality of Life /ADL/ Function	Caregiver Burden	Other
ADAS-Cog (also ADAS-11) AMTS BCRS CamCOG CASI CETM IQCODE MCPT MMSE MMMSE SMMSE CMMSE MQ RMT RVM SIB SMQ SMST TP,TPAT WAIS	ACPT Babcock Story recall Barbizet Visuospatial BLM BNT BSRT BSV BVR CCASSS Category Fluency CDT CNTB Controlled Challenge Word Association COWAT CVLT Digit Span Test DSST EFR FCMT FIGT FOM GAGS Grooved Pegboard Test Letter Cancellation Letter Fluency LMT LNNB MAE MEMT MNLT NCT NDT NLT NMIC NST OLT OMDR	R-AVL RM RPM Rey Memory Test Set test Snodgrass Picture Naming Task SRT-DR SWFIT SWFT SKT TK TMT WMS (MQ) WMS-RR ZVT	ADAS ADCS-CGIC ADS AGS-E Bf-S BGP Blessed-D/ BDRS CAPE CDR-NH CDR-SB CGAE CGI CGIC CGRS CIBIC CICIC+ DBDS DMR DRS EIS FCCA FRS GERRI GBS GDS GIS GPI-E HDS HIS MAC-F NOSGER NOSIE NPI (NPI-4, NPI10) PDRS PGIR Plutchik CGS RAGS RGRS SCAG Stockton GRS TSI VRGI	ABID ABSR ACES ADAS-Non-cog AFBS BDI BEHAVE-AD BPRS BRMS BRDS CERAD-BRSD CMAI CS or CSDD DSCS DSS Facial Behavior GS HAM-A HAM-D HDRS HDS-R IPSC-E LPRS MAACL-R MADRS MOSES NAB NMS NOSGER-IADL NPI-NH NSL OAS PANSS-EC POMS RMBPC RPT SBI SHGRT SRT VHB	ABS ADCS-ADL ADFACS ADL ADL-C ADL-PDS BI Dependency Scale DAD FAST FIM IADL IDDD NAA NAI OARS-ADL PDS PSMS PSQI QoL QoL-P QoL-C SF-36 SIP Time to functional decline	CATS CSS CSI SCB	CAUST SAS AIMS BARS/ BAS ERP ESRS Finger Tapping Test SAS UPDR

Summary Evidence Tables

Summary Table 1. Carnitine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ADL	Caregiver Burden	Other
Livingston, 1991	NS*	MX*	NT	NT	NS*	NT	NT
Rai, 1989	NT	NS*	NS*	NT	NS*	NT	NT
Sano, 1992	NS*	NS*	NT	NT	NS*	NT	NT
Spagnoli, 1991	NT	MX	MX	NS	NT	NT	NT
Thal, 2000a	NS	NT	NS	2º NS	2º NS	NT	NT
Thal, 1996a Brooks, 1998	NS	NT	NS	2º NS	2º NS	SUBGROUP	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 2. Donepezil.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ADL	Caregiver Burden	Other
Burns, 1999	SC	NT	SC	NT	SC	NT	NT
Feldman, 2001 Gauthier, 2002	2º SC	NT	SC	NR	2º SC	NR	SUBGROUP
Mohs, 2001	SC	NT	NT	NT	SC	NT	SC Time to functional decline
Prasher, 2002	2º NS*	NT	NS*	2º MX*	NT	NT	NT
Rogers, 1996 Rogers, 2000 Neumann, 1999 Rogers, 1998	SC	NT	SC	NT	2ºMX	NT	NT
Rogers, 1998b Doody, 2001 Sparano, 1998	SC	NT	SC	NT	2º NS	NT	NT
Rogers, 1998a Doody, 2001 Steele, 1999	SC	NT	SC	NT	2º SC	NT	NT
Tariot, 2001	2º NS	NT	2º SC	NS	2º NS	NT	SUBGROUP
Winblad,2001	2º SC	NT	SC	2º NS	2º SC	NT	SUBGROUP
Pratt, 2002	SC	NT	SC	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2º Secondary outcome
* OC analysis

Summary Table 3. Galantamine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ADL	Caregiver Burden	Other
Erkinjuntti, 2002	SC*	NT	SC*	2ºSC*	2ºSC*	NT	NT
Raskind, 2000	SC	NT	SC	NT	2ºNS	NT	NT
Rockwood, 2001	SC	NT	SC	NS	2ºSC	NT	NT
Tariot, 2000	SC	NT	SC	SC	SC	NT	NT
Wilcock, 2000 Wilcock, 2001	SC	NT	SC	NT	SC	NT	NT
Wilkinson, 2001	MX	NT	2ºNS	NT	2ºNS	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 4. Metrifonate.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL n	Caregiver Burden	Other
Becker, 1996	SC*	NT	2^{o}MX*	2^{o}NS*	2^{o}NS*	NT	NT
Becker, 1998	SC*	NT	2^{o}NS*	2^{o}NS*	2^{o}NS*	NT	NT
Cummings, 1997	SC*	NT	SC*	NT	NT	NT	NT
Cummings, 1998b Cummings, 1998a	SC	NT	SC	NT	2^{o}NS	NT	NT
Dubois, 1999 McKeith, 1998	SC	NT	SC	2^{o}SC	2^{o}SC	NT	NT
Jann, 1999	SC	NT	2^{o}MX	2^{o}NS	NT	NT	NT
Morris, 1998	SC	NT	SC	2^{o}NS	2^{o}NS	NT	NT
Pettigrew, 1998	NR	NT	NR	NR	NT	NT	NT
Raskind, 1999	SC	NT	MX	MX	NS	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 5. Nicergoline.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Herrmann, 1997	SC	NT	SC	NT	NT	NT	NT
Nappi, 1997	SC*	NT	SC*	NT	NT	NT	NT
Saletu, 1995 Saletu, 1997	SC*	NT	MX*	NS*	NT	NT	SUBGROUP
Winblad, 2001a	SC	NT	NS	2^{o}NS	2^{o}NS	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 6. Physostigmine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Van Dyck, 2000	SC	NT	MX	NT	2^{o}NS	NT	NT
Moller, 1999	NR	NT	NS*	NR	NT	NT	NT
Thal, 1996b	SC	NT	SC	NT	2^{o}NS	NT	NT
Thal, 1999	SC	NT	SC	NT	2^{o}NS	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 7. Posatirelin.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Ferrari, 1998	SC	NT	SC	NS	SC	NT	SUBGROUP
Gasbarrini, 1997	SC	NT	NT	SC	SC	NT	NT
Parnetti, 1995	NR	NT	NT	NR	NR	NT	NT
Parnetti, 1996	MX*	NT	NT	NS*	SC*	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 8. Rivastigmine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Agid, 1998	NR	SC*	SC*	NS*	NS*	NT	NT
Corey-Bloom, 1998 Farlow, 2001 Farlow, 2000 Kumar, 2000 Del Ser, 2000 Doraiswamy, 2002	SC	NT	SC	NT	SC	NT	NT
Forette, 1999	SC*	NT	SC*	NS*	NS*	NT	NT
McKeith, 2000	SC	NT	NS	MX	NT	NT	NT
Potkin, 2001	NT	NS*	SC*	NT	NT	NT	NT
Rosler, 1999 Rosler, 2001 Farlow, 2000 Rosler, 1998 Doraiswamy, 2002	SC	NT	SC	NT	SC	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^o Secondary outcome
* OC analysis

Summary Table 9. Tacrine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Knapp, 1994b Farlow, 1998 Gracon, 1996 Henke, 1997 Knapp, 1994a Knopman, 1996 Raskind, 1997 Schneider, 1997 Schneider, 1996 Smith, 1996	SC	NT	SC	NS	NT	NT	NT
Maltby, 1994	NS*	NS*	NT	NS*	NS*	NS*	NT
Prentice, 1996	NS*	NT	NT	NS*	NT	NT	NT
Weinstein, 1991 Gool, 1991	NS*	NT	NT	NT	NS*	NS*	NT
Wong, 1999	MX	NT	NS	NT	NT	NT	NT
Wood, 1994	NS	NT	SC	NS	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 10. Velnacrine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Zemlan, 1996	SC*	NT	SC*	2^{o}NS*	2^{o}NS*	NT	NT
Antuono, 1995	SC	NT	SC	NT	2^{o}SC	2^{o}SC	NT
Huff, 1991	NT	NS*	MX*	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 11. Various cholinergic neurotransmitter modifying agents.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
CHOLINERGIC NEUROTRANSMITTER MODIFYING AGENTS							
Eptastigmine							
Imbimbo, 1999	SC	NT	SC	NT	SC	NT	NT
Canal, 1996	NS*	NS*	MX*	NT	MX*	NT	NT
Huperzine							
Xu, 1995	SC*	NT	NT	SC*	SC*	NT	NT
Linopirdine							
Van Dyck, 1997	NS*	NT	NS*	NS*	NT	NT	NT
Rockwood, 1997 Rockwood, 2000	SC	2^{o}NS	NS	2^{o}NS	2^{o}NS	NT	NT
Sabeluzole							
Mohr, 1997	NS*	NS*	NT	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 12. Haloperidol.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver/ Burden	Other
Allain, 2000	2^{o}NS	NT	2^{o} SC	SC	NT	NT	NT
Auchus, 1997	NT	NT	NT	NS*	NT	2^{o} NS*	NT
De Deyn, 1999	NR	NT	NR	SC	NR	NT	NT
Petrie, 1982	NT	NT	NR	SC*	NT	NT	NT
Teri, 2000	NS*	NT	NS*	NS*	SC* favors Placebo	NS*	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 13. Memantine.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Orgogozo, 2002	SC	NT	NS	NT	NT	NT	NT
Wilcock, 2002	SC	NT	NS	NT	NT	NT	NT
Winblad, 1999	NT	NT	SC	SC	SC	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 14. Selegeline.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Agnoli, 1992	MX*	NT	NT	NT	NT	NT	NT
Burke, 1993a Burke, 1993b	NS*	NT	NS*	NS*	NT	NT	NT
Filip, 1999	MX*	NT	MX*	NT	NT	NT	SUBGROUP
Freedman, 1998	2^o NS	2^o NS	2^o NS	NS	NT	NT	NT
Mangoni, 1991 Smirne, 1993	NR	SC*	SC*	SC*	NT	NT	NT
Sano, 1997 Sano, 1996	NT	NT	NT	NT	NT	NT	NS Survival SUBGROUP

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^o Secondary outcome
* OC analysis

Summary Table 15. Various non-cholinergic neurotransmitter/neuropeptide modifying agents.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Perphenazine							
Pollock, 2002	NR	NT	NT	NS	NR	NR	NT
Thioridazine							
Barnes, 1982	NT	NT	NS	NS	NT	NT	NT
Alaproclate							
Dehlin, 1985	NS	NT	NT	NS	SC	NT	NT
Anapsos							
Alvarez, 2000	SC*	NT	NT	NT	NT	NT	SUBGROUPS
Cutler, 1993	NR*	NT	NS*	NT	NT	NT	NT
Citalopram							
Nyth, 1990	NT	NT	MX*	NS*	NT	NT	NT
Pollock, 2002	NT	NT	NT	SC	NT	NT	NT
Divalproex Sodium							
Tariot, 2001b	2^o NS	NT	2^o SC favors Placebo	NS	NT	NT	NT
Porsteinsson, 2001	2^o NS*	NT	2^o NS*	NS*	2^o NS*	NT	NT
Fluvoxamine							
Olafsson, 1992	NS*	NS*	NS*	NT	NT	NT	NT
Fluoxetine							
Petracca, 2001	NS	NT	NR	NS	NS	NT	NT
Auchus, 1997	NT	NT	NT	NS	NT	2^oNS	NT
Imipramine							
Reifler, 1989	NS*	NT	SC*	NS*	NS*	NT	SUBGROUPS
Lisuride							
Claus, 1998	SC*	NS*	NS*	NS*	NT	NT	NT
Lorazepam							
Meehan, 2002 Clark, 2001 Kennedy, 2001 Mintzer, 2001 Street, 2001	2^o NS*	NT	2^o NS*	NS*	NT	NT	NT
Loxapine							
Barnes, 1982	NT	NT	NS	NS	NT	NT	NT
Petrie, 1982	NT	NT	NR	SC*	NT	NT	NT
LU25							

MX Mixed results NT Not tested 2^o Secondary outcome

NS Not statistically significant SC Significant change * OC analysis

Summary Table 15. Various non-cholinergic neurotransmitter/neuropeptide modifying agents.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Thal, 2000b	NS	NT	NS	2° NS	2° NS	NT	NT
Maprotiline							
Fuchs, 1993	2° NS*	NT	NS*	NT	NT	NT	NT
Minaprine							
Passeri, 1987	NT	NT	NT	MX	NT	NT	NT
Moclobemide							
Roth, 1996	SC	NT	MX	SC	NT	NT	NT
Naftidrofuryl							
Moller, 2001	SC	NT	SC	NT	NT	NT	NT
Olanzapine							
Meehan, 2002	2° NS*	NT	2° NS*	SC*	NT	NT	NT
Street, 2000	2° NS	NT	NT	SC	NT	NT	NT
Phosphatidylserine							
Amaducci, 1988 SMID Group, 1987 Amaducci, 1986	SC*	SC*	SC*	NT	NT	NT	SUBGROUP
Crook, 1992a	NT	NT	SC	NT	2° NS	NT	NT
Risperidone							
Katz, 1999 Jeste, 2000 Pryse-Phillips, 2000	NT	NT	2° SC	SC	NT	NT	NT
De Deyn, 1999	NS	NT	SC	MX	NS	NT	NT
Sertraline							
Lyketsos, 2000	2° NS	NT	SC	2° MX	2° SC	NT	NT
Magai, 2000	NS	NT	NT	NS	NT	NT	NT
Tiapride							
Allain, 2000	NR	NT	NR	2° SC	NT	NT	NT
Trazodone							
Teri, 2000	NS*	NT	NS*	NS*	SC*	NS*	NT
Xanomeline							
Bodick, 1997 Veroff, 1998 Satlin, 1997	SC	2° SC	SC	NT	2° SC	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2° Secondary outcome
* OC analysis

Summary Table 16. Cerebrolysin.

Author, Year	General Cognitive Function Meausre	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Bae, 2000	SC	NT	SC	NT	2^o NS	NT	NT
Panisset, 2002	NS*	NT	SC*	NT	2^o NS*	NT	NT
Ruther, 2001 Ruther, 2002	SC	NR	SC	2^o SC	NR	NT	NT
Ruther,1994 Ruther, 2000	NT	SC	SC	NR	2^o NS	NT	NT
Xiao, 2000	SC	2^o MX	SC	NT	2^o MX	NT	NT
Xiao, 1999	SC	2^o SC	NS	2^o NS	2^o NS	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^o Secondary outcome
* OC analysis

Summary Table 17. Estrogens.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Asthana, 2001	NT	SC	2^{o}NS*	NR	2^{o}NS*	NT	NT
Henderson, 2000	NS*	NT	2^{o}NS*	2^{o} NS*	2^{o}NS*	NT	NT
Kyomen, 1999 Kyomen, 2002	NT	NR	NS*	MX*	NS*	NT	NT
Mulnard, 2000	2^{o} NS	2^{o} MX	NS	2^{o} NS	2^{o} NS	NT	NT
Wang, 2000	NS	NT	NS	2^{o} NS	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 18. Ginkgo Biloba.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver/ Burden	Other
Kanowski, 1996	NT	SC	SC	NS	NT	NT	NT
Le Bars, 1997 Le Bars, 2000 Le Bars, 2002 Por, 1998	SC	NT	MX	NT	NT	NT	NT
Maurer, 1997	2^o NS	SC	2^o NS	NR	NT	NT	NT

MX Mixed results NT Not tested 2^o Secondary outcome
NS Not statistically significant SC Significant change * OC analysis

Summary Table 19. Idebenone.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Bergamasco, 1994	NT	MX*	SC*	NT	NT	NT	NT
Gutzmann, 1998 Weyer, 1996	2^{o} SC	NT	SC	NT	2^{o} SC	NT	NT
Marigliano, 1992	SC*	NT	NT	NT	SC*	NT	NT
Weyer, 1997	2^{o} SC	NT	SC	2^{o} SC	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 20. Oxiracetam.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Bottini, 1992	NT	MX*	NT	NT	SC*	NT	NT
Maina, 1989	SC*	NT	SC*	SC*	NT	NT	NT
Mangoni, 1988	NT	SC*	NT	SC*	NT	NT	NT
Rozzini, 1992 Rozzini, 1993	NR	NR	NT	NR	NS*	NT	NT
Villardita, 1992	SC*	MX*	NT	NS*	SC*	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 21. Pentoxifylline.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Black, 1992	2^{o} NS*	NT	NS*	2^{o} NS*	NT	NT	SUBGROUP
Ghose, 1987	MX	2^{o} NS*	NS*	NT	NT	NT	SUBGROUP
Knezevic, 1996	2^{o} NS	NT	NS	2^{o} NS	2^{o} NS	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 22. Propentofylline.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Marcusson, 1997	2^{o} SC	SC	MX	2^{o} SC	2^{o} NS	NT	NT
Mielke, 1998	NS*	NS*	NT	NT	NT	NT	NT
Mielke, 1996	NS*	NS*	NT	NT	NT	NT	NT
Saletu, 1990 Moller, 1994	SC*	NS*	SC*	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 23. Additional pharmacological agents.

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
ACTH Neuropeptides							
Soininen, 1985 Partanen, 1986	NT	NT	NS*	NT	NT	NT	NT
Kragh-Sorensen, 1986	NT	SC*	SC*	NT	NT	NT	NT
Aniracetam							
Senin, 1991	SC*	SC*	SC*	NT	NT	NT	NT
Ateriod							
Ban, 1991b	SC*	NT	MX*	NS*	NT	NT	NT
Buflomedil							
Cucinotta, 1992	NT	NR	NR	NR	NT	NT	NT
Choto-san							
Shimada, 1994	NT	NT	MX*	SC*	NT	NT	NT
Terasawa, 1997	NT	NT	SC*	NS*	NT	NT	NT
Citicoline							
Parnetti, 1995	NR	NT	NT	NR	NR	NT	NT
Cyclandelate							
Schellenberg, 1997	NT	MX	SC	SC	NT	NT	NT
Weyer, 2000	NS	NT	NS	NT	NS	NT	NT
DDAVP (Deamino-D-arginine-vasopressin)							
Peabody, 1986	NS*	NT	MX*	MX*	NT	NT	NT
Denbufylline							
Treves, 1999	NS*	NS*	NT	NT	NT	NT	NT
Desferrioxamine							
Crapper -McLachlan, 1991	NT	NT	NT	SC*	NT	NT	NT
Diclofenac/misoprostol							
Scharf, 1999	NS	NT	NS	2^{o} NS	2^{o} NS	NT	NT
Ergokryptine							
Cucinotta, 1996 Cucinotta, 1998	2^{o} SC	2^{o} SC	MX	NR	NT	NT	NT
Danielczyk, 1988	NS*	NR	SC*	MX*	NS*	NT	NT
Glycosaminoglycan polysulfate							
Ban, 1991a	MX*	NT	MX*	SC*	NS*	NT	NT
Guanfacine							
Crook, 1992b	NR	SC	SC	NT	NT	NT	NT
Hydergine							

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Thompson, 1990	MX*	NT	MX*	NS*	NT	NT	NT
Hydroxchloroquine							
Van Gool, 2001	2^{o} NS	NT	NT	2^{o} NS	NS	NT	NT
Aisen, 2002b	NS	NT	NS	NS	NS	NT	NT
Indomethacin							
Rogers, 1993	NS*	MX*	NS	NT	NT	NT	NT
Monosialotetrahexosylgan GM1							
Ala, 1990	NS*	NS*	NS*	NS*	NS*	NT	NT
NAC (N-Acetylcysteine)							
Adair, 2001	NS	2^{o}NS	NT	NT	NS	NT	NT
Nimodipine							
Pantoni, 2000a	NS	NS	NS	NT	NS	NT	NT
Ban, 1990	SC*	SC*	SC*	SC*	NT	NT	NT
Nizatidine							
Carlson, 2002 Breitner, 1999	NT	NS	NT	NT	NS	NT	NT
Nootropic agent - BMY							
Shrotriya, 1996	SC*	NT	NS*	NT	NT	NT	NT
Piracetam							
Croisile, 1993	NS*	NS*	NS*	NS*	NT	NT	NT
Prednisone							
Aisen, 2000b Aisen, 2000a	NS	NT	2^{o} NS	2^{o} MX	NT	NT	NT
Simvastatin							
Simons, 2002	MX*	NT	NT	NT	NT	NT	NT
Thiamine							
Nolan, 1991	SC*	SC*	NT	NT	NT	NT	NT
Vincamine							
Fischhof, 1996	NT	NR	SC*	NT	NR	NT	SUBGROUP
Vitamin E							
Sano, 1997 Sano, 1996	NT	NT	NT	NT	NT	NT	SC Institutionalization SUBGROUP
Xantinolnicotinate							
Kanowski, 1990	NT	SC*	SC*	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 24. Drug vs drug studies

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Haloperidol / Tradozone							
Teri, 2000	NS	NT	NS	NR	NR	NR	NT
Olanzepine / Lorazepam							
Meehan, 2002	NR	NT	NT	NT	NT	NT	NT
Haloperidol/Loxapine							
Carlyle, 1993	NT	NT	NT	NS*	NT	NT	NT
Alprazolam / Lorazepam							
Ancill, 1991	NT	NT	NS*	NT	NT	NT	NT
Haloperidol / Oxazepam / Diphenydramine							
Coccaro, 1990	NT	NT	NS*	NS*	NS*	NT	NT
Sulphomucopolysaccharides / CDP-choline							
Cucinotta, 1987	NT	MX*	SC* favors sulphomucopoly saccarides	SC* favors sulphomucopol ysaccarides	NT	NT	NT
Citalopram / Mianserin							
Karlsson, 2000	NT	NT	NT	NS*	NT	NT	NT
Citalopram/Perphenazine							
Pollock, 2002	NR	NT	NT	NR	NR	NR	NT
Thoridazine / Loxapine							
Barnes, 1982	NT	NT	NS	NR	NT	NT	NT
Tiapride / Haloperidol							
Allain, 2000	2^{o} NS	NT	2^{o} S	NS	NT	NT	NT
Tacrine / Silymarin							
Allain, 1998	NR	NR	NT	NT	NT	NT	NT
Risperidone / Haloperidol							
Chan, 2001	NR	NT	NT	NS*	NR	NT	NT
De Deyn, 1999	NR	NT	NR	NR	NR	NT	NT
Paroxetine / Imipramine							
Katona, 1998	NT	NT	NS	NS	NT	NT	NT
Fluoxetine / Amitriptyline							
Taragano, 1997	NS*	NT	NT	NS*	NT	NT	NT
Selegiline / Alpha-Tocopherol							
Sano, 1997 Sano, 1996	NT	NT	NT	NT	NT	NT	NR
Meclofenoxate / Antagonic Stress							

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 24. Drug vs drug studies

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Popa, 1994	SC* favors Antagonic Stress	SC* favors Antagonic Stress	SC* favors Antagonic Stress	NT	NT	NT	NT
Posatirelin / Citicoline							
Parnetti, 1995	SC* favors Posatirelin	NT	NT	SC* favors Posatirelin	NR	NT	NT
Pyritinol / Hydergine							
Spilich, 1996	NR	NT	SC* favors Pyritinol	NT	NT	NT	NT
Donepezil / Vitamin E							
Thomas, 2001	SC* favors Donepezil	NT	NT	NR	NT	NT	NT
Sulodexide / Pentoxilylline							
Parnetti, 1997	NR	NT	NT	NR	NR	NT	NT
Haloperidol / Fluoxetine							
Auchus, 1997	NT	NT	NT	NS*	NT	2^{o} NS*	NT
Melperone / Tiapride							
Gutzmann, 1997	NT	NT	NS	NR	NR	NT	NT
Idebenone/Tacrine							
Gutzmann, 2002	NS	NT	SC favors Idebenone	NR	NT	NT	NT
Nicergoline/Antagonic Stress							
Schneider, 1994	SC* favors Antagonic Stress	NT	SC* favors Antagonic Stress	NT	NT	NT	NT
Tradozone / 5'-MTHF Folate							
Passeri, 1993	NR	NT	NT	NR	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 25. VaD/MID Studies

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Ban, 1991b Ateroid Subgroup MID	SC*	NT	MX*	NS*	NT	NT	NT
Cucinotta, 1992 Buflomedil VaD	NT	NR	NR	NR	NT	NT	NT
Cucinotta, 1987 sulphomucopolysaccarides vs CDP-choline MID	NS	SC*	SC* favors sulphomucopoly saccarides	SC* favors sulphomucopoly saccarides	NT	NT	NT
Xiao, 1999 Cerebrolysin VaD	SC	2^{o} SC	NS	2^{o} NS	2^{o} NS	NT	NT
Shimada, 1994 Choto-san VaD	NT	NT	MX*	SC*	NT	NT	NT
Terasawa, 1997 Choto-san VaD	NT	NT	SC*	NS*	NT	NT	NT
Nyth, 1990 Citalopram Subgroup VaD	NT	NT	NS*	NS*	NT	NT	NT
Pratt, 2002 Donepezil VaD	SC	NT	SC	NT	NT	NT	NT
Kanowski, 1996 Ginkgo Biloba Subgroup MID	NT	NR	NR	NR	NT	NT	NT
Marigliano, 1992 Idebenone MID	SC*	NT	NT	NT	SC*	NT	NT
Orgogozo, 2002 Memantine VaD	SC	NT	NS	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Summary Table 25. VaD/MID Studies

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Wilcock, 2002 Memantine VaD	SC	NT	NS	NT	NT	NT	NT
Winblad, 1999 Memantine Subgroup HIS>/= 5	NT	NT	2^o SC*	NT	NT	NT	NT
Passeri 1987 Minaprine Subgroup MID	NT	NT	NT	MX	NT	NT	NT
Herrmann, 1997 Nicergoline MID	SC	NT	SC	NT	NT	NT	NT
Saletu1995 Saletu1997 Nicergoline Subgroup MID	SC*	NT	MX*	NS*	NT	NT	NT
Pantoni, 2000a Nimodipine MID	NS	NS	NS	NT	NS	NT	NT
Maina, 1989 Oxiracetam Subgroup MID	NT	NR	NR	NR	NT	NT	NT
Knezevic, 1996 Pentoxifylline MID	2^o NS	NT	NS	2^o NS	2^o NS	NT	NT
Black, 1992 Pentoxifylline Vascular damage or strokes	2^o NS*	NT	NS*	2^o NS*	NT	NT	SUBGROUP
Parnetti, 1997 Pentoxifylline vs Sulodexide VaD	NR	NT	NT	NR	NR	NT	NT
Ghose 1987 Pentoxyfylline Subgroup MID	SC*	NS*	NS*	NT	NT	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^o Secondary outcome
* OC analysis

Summary Table 25. VaD/MID Studies

Author, Year	General Cognitive Function Measure	Specific Cognitive Function Measure	Global Assessment	Behavior/ Mood	Quality of Life/ ADL	Caregiver Burden	Other
Parnetti, 1996 Posatirelin VaD	MX*	NT	NT	NS*	SC*	NT	NT
Ferrari 1998 Posatirelin Subgroup VaD	NT	NT	NR	NT	NT	NT	NT
Mielke, 1996 Propentofylline VaD	NS*	NS*	NT	NT	NT	NT	NT
Marcusson 1997 Propentofylline Subgroup VaD	NT	SC	SC	NR	NR	NT	NT
Passeri 1993 5'-MTHF vs Tradozone Subgroup MID	NT	NR	NT	NR	NT	NT	NT
Fischhof, 1996 Vincamine Subgroup MID	NT	NR	SC*	NT	NR	NT	NT

MX Mixed results
NS Not statistically significant
NT Not tested
SC Significant change
2^{o} Secondary outcome
* OC analysis

Chapter 4. Discussion

This systematic review was undertaken primarily to evaluate the efficacy of pharmacological agents in the treatment of dementia. The studies were limited to parallel design RCTs with quality scores greater than 3 on the Jadad scale. The interventions were not limited to those currently on label by the FDA; it was of interest to cast a wide net and capture reports of pharmacological agents that are used off-label for the treatment of dementia. Since a variety of agents with different therapeutic effects were evaluated, the outcomes were not restricted to a specific subset of all available outcomes used in the dementia literature. The psychometric properties of some of the most commonly used outcomes have been critically appraised and found to be limited. Moreover, there is no current consensus as to which domains, and the outcomes within these, that best reflect clinically important change.

Strength of the Evidence

The studies eligible for review in this dementia report represent the highest form of evidence. This strongly suggests that these trials are more likely to be "well-designed, well conducted studies in representative populations that assess the effects of health outcomes".[53] The high quality scores also indicate that the studies evaluated in this systematic review have a relatively high level of internal validity. The characteristics of the population and the interventions were detailed to assist the reader in evaluating the degree of external validity. Similarly, attempts were made to highlight "consistency" in the evidence as well as the quantity of evidence and the magnitude of the reported changes.

Although, there is greater understanding on evaluating the evidence for the "benefits" of therapies, there is less clarity on determining the potential for harms from pharmacological interventions for treating dementia. With respect to adverse events and the potential for serious harms, greater variability in systematic collection and reporting of these were observed in the dementia pharmacological literature. Evaluation of the potential for harm is considered with three main points: 1) the most frequently reported adverse events across studies for a specific drug, 2) the overall withdrawal rate due to adverse events for both the control and treatment groups, and 3) the range of frequencies reported for a subset of symptoms (nausea, diarrhea, dizziness, agitation, eating disorder) selected **a priori** and evaluated for all pharmacological interventions.

At present there is no coherent framework that captures the disease processes present in dementia patients for the range of outcomes evaluated in this systematic review. This report details the highest evidence from both a design and internal validity perspective. It is our view that determining the clinical relevance (external validity) of such high-quality evidence must ultimately be reached by consensus amongst multidisciplinary experts within the decision-making body that will use this evidence for such purposes as developing practice guidelines.

Question 1: Does pharmacotherapy for dementia syndromes improve cognitive symptoms and outcomes?

Summary of the Systematic Review Results

A total of 97 interventions in 186 studies were eligible for evaluation in this systematic review and were distributed as follows:

- A total of 16 different cholinergic neurotransmitter modifying pharmacological agents in 72 studies.
- A total of 35 non-cholinergic neurotransmitter/neuropeptide modifying agents in 61 studies.
- A total of 46 other pharmacological agents in 76 studies*.

* there are more than 186 studies here because some studies compared a drug from one class with a drug from another, so that study would be in both categories and therefore counted twice.

- two studies compared two NCNMAs with an OTHER.
- two studies compared a CNMA with an OTHER.
- one study compared a CNMA with two OTHERS.
- two studies compared an NCNMA with an OTHER.

The evidence for all these pharmacological agents was presented in great detail in Chapter 3 and in Evidence Tables of Key Study Characteristics, Tables of Study Results, and Tables of Study Adverse Events contained in Appendix C. Conclusions regarding those pharmacological agents that had a minimum of three trials are summarized here. The summary of the pharmacological agents that had fewer than three trials can be found in Chapter 3.

Summary of Cholinergic Neurotransmitter Modifying Agents

Carnitine. Six trials evaluated carnitine in 925 subjects with mild to moderate severity, recruited predominately from the community at doses of 2 to 3 g for either 24 or 52 weeks. Evidence of benefit is conflicting for the domains of cognition. Most studies were not statistically significant and the lack of sufficient power may have been an important factor. Similarly, no significant differences were found in the domains of global assessment, behavior/mood, and quality of life/ADL; power could not be evaluated for the majority of these outcomes.

Four of the six studies scored 3 for quality on reporting adverse events. Withdrawal rates due to adverse events varied from 0 - 3% (excluding results from one outlier trial[248]), and gastrointestinal symptoms were the most frequently reported types of adverse events. The percent of subjects reporting the a priori symptoms of interest across all studies were as follows: 1) nausea (placebo = 6 - 14%, all doses carnitine = 28%), and 2) agitation (placebo = 6%, all doses carnitine = 7%). Dizziness, diarrhea, or eating disorder were not reported by any study. No serious adverse events requiring hospitalization and associated with carnitine were reported.

Donepezil. Ten trials in 3239 subjects evaluated the efficacy of donepezil compared to placebo, and one trial compared donepezil to a group given vitamin E. The majority of studies (n = 8) evaluated AD patients, for which half were recruited from the community (other studies did not specify). The subjects had predominately mild to moderate disease and doses of 5 or 10 mg were used with varying duration from 12 to 56 weeks.

There is consistent evidence of benefit in the domains of general cognitive function and global assessment. The combined effect sizes for the ADAS-cog and the CIBIC were estimated. Evidence is inconsistent for a dose response in these domains based on the three studies that evaluated two different doses (5 and 10 mg); the benefit was of similar magnitude for both dose groups for global assessment outcomes. Similarly, two of the three studies that evaluated behavior/mood outcomes (NPI) showed no statistically significant changes relative to placebo; these trials lacked sufficient power to detect a difference. There is some evidence of benefit in ADL outcomes, although this outcome domain was evaluated with a variety of instruments. Caregiver burden outcomes was evaluated in a single study that did not report the findings for this domain.

Adverse events quality scores were 3 or greater for the majority of studies (n=7). Four trials provided evidence of a dose response for adverse events. One study showed a statistical difference for balance-related problems and asthenia (neurological fatigue) between placebo and treatment groups. Withdrawal due to adverse events ranged from 0 - 18% for treatment groups and 0 – 11% for placebo. Four out of six studies testing differences between groups were statistically significant for diarrhea (placebo = 3 - 21%, all doses donepezil = 0 - 38%), nausea and vomiting (placebo = 4 - 9%, all doses donepezil = 4 - 25%). The other a priori symptom reported was agitation and frequencies for placebo varied from 0 - 8% and for all doses from 3 - 19%; but these were not shown to be statistically different.

Galantamine. Six trials in 3530 subjects evaluated the efficacy of galantamine compared to placebo. Doses of 24 and 32 mg were evaluated in half of these studies. Five studies evaluated AD patients and there was limited information regarding whether the subjects were from the general community or institutional settings. All studies recruited subjects with mild to moderate disease and the drug was administered with varying duration of 3 or 6 months.

Evidence of benefit is consistent in the domains of general cognitive function, global assessment, quality of life/ADL. Two of the three studies that evaluated, behavior/mood found statistically significant differences. A small dose effect was evident in the ADL domain when comparing the pooled estimates of the DAD; no dose effect was observed for outcomes in the global assessment domain, and dose effect could not be evaluated for the general cognition domain. The caregiver burden domain was not evaluated in any trials.

Five of the six trials scored 3 out of 5 on our quality scale for rating adverse events. Withdrawal rates due to adverse events ranged from 4 - 9% for placebo and 8 - 27% for the treatment group. One study showed a dose response for adverse events. Although, most trials did not report testing for differences between groups, two trials reported a statistically significant

difference in weight loss with the treatment group having more than the placebo group. The most common types of adverse events reported were gastrointestinal symptoms (nausea and vomiting, diarrhea), eating disorders/weight loss, and dizziness. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea and vomiting (placebo = 3 - 13%, all doses = 6 - 44%), 2) dizziness (placebo = 3 - 11%, all doses = 4 - 19%), 3) diarrhea (placebo = 2 - 10%, all doses = 4 - 19%), 4) agitation (placebo = 1 - 9%, all doses = 6 - 15%), and 5) eating disorder (placebo = 0 - 6%, all doses = 4 - 20%).

Metrifonate. Nine studies compared metrifonate to placebo in 2759 subjects with mild to moderate AD (likely from community settings as the majority of studies did not specify this). Metrifonate dosages evaluated varied from 50 to 80 mg, and study duration ranged from 21 days to 26 weeks duration.

All but one study showed metrifonate to have a consistent positive effect on measures of general cognitive function; none of the studies evaluated any specific cognitive function measures. The effects on global assessment were less consistent, but suggested a positive effect in four of the eight studies that reported this outcome. Evidence for effect in the domains of behavior/mood and quality of life/ADL were not significant in the majority of studies that evaluated these domains, however these were primarily evaluated as secondary outcomes and likely lacked sufficient power.

With the exception of a single study, quality scores for reporting adverse events were greater than 3. However, only one trial[83] tested for differences between groups and found nausea and vomiting, diarrhea, and muscle and joint disorder to be significantly different. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea and vomiting (placebo = 3 - 14%, all doses = 2 - 50%), 2) dizziness (placebo = 1%, all doses = 3 - 4%), 3) diarrhea (placebo = 4 - 14%, all doses = 11 - 19%), 4) agitation (placebo = 2 - 14%, all doses = 8 - 33%), and none reported eating disorder as an adverse event. Withdrawal due to adverse events varied from 0 - 9% for placebo and 0 - 12% for the treatment group. Overall, it was difficult to determine which types of adverse events reported had the potential to cause serious harm. This is noteworthy as metrifonate has been withdrawn from use in North America, and Bayer has suspended Phase III trials,[87] because some patients in clinical trials have experienced serious muscle weakness . This decision was based on the results of an experimental study showing risk of respiratory paralysis with the use of metrifonate. Other adverse events of concern included severe leg cramps, dyspepsia, and bradycardia. None of the studies we reviewed indicated that if present, these events differed significantly between groups. It is not clear if this inconsistency is a function of the methods used to collect and report adverse events or a limitation of RCTs as a source of detecting serious adverse events when incidence is low.

Nicergoline. Four trials in 705 subjects compared nicergoline to placebo and one trial compared it to antagonic-stress in mixed populations that included AD, MID, PDD, VaD, mixed dementia, and SDAT, which were classified as mild to moderate in severity.

All placebo-controlled trials found a positive effect for general cognitive outcomes, but half the results were based on OC analyses. The evidence was mixed for benefit in the domain of global assessments. No significant differences were found for behavior/mood, and quality of life/ADL outcomes, but these were evaluated in few studies and as secondary outcomes (suggesting that sufficient power was an issue).

Quality scores for reporting adverse events varied from 2 to 5 for these four trials, and none tested for differences between groups. Withdrawal due to adverse events varied from 0 - 8% for placebo and 0 - 9% for the treatment group. With the exception of headache, which was reported in all four trials, it was difficult to determine which types of adverse events most characterized exposure to this pharmacological agent. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = 3%), 2) dizziness (placebo = 1-2%, all doses = 0% or not reported), 3) diarrhea (placebo = 2 - 6%, all doses = 2 - 4%), 4) agitation (placebo = 5%, all doses = not reported), and none reported eating disorder as an adverse event.

Physostigmine. Four studies of 1198 subjects with mild to moderate AD evaluated physostigmine administered in patch and oral form (30 to 60 mg dose) for study duration varying from 6 to 24 weeks. All subjects were recruited from the community.

There is evidence that physostigmine has a statistically significant effect on general cognitive function, as three of the four studies showed improvement. Evidence for an effect on global function was mixed with no consistent benefit. Similarly, for quality of life/ADL outcomes, all three studies that evaluated this domain were not statistically significant but these were secondary outcomes and may reflect a lack of power. Behavior/mood and caregiver burden were not tested in these trials.

The quality scores for reporting adverse events were generally low, scoring 1 or 2 out of 5. Withdrawal rates due to adverse events varied from 1 - 5% for placebo and 12 - 55% in the treatment group, with one study not reporting rates. The high withdrawal rates were in studies with sample sizes that varied from181 to 475 subjects. A single study tested for differences between groups, and found that dizziness, tremor, weight loss, asthenia, confusion, delirium, and respiratory problems were significantly different. The cluster of reported types of adverse events suggests that gastrointestinal problems (abdominal pain, diarrhea) (placebo = 1 - 9%, all doses = 13 - 28%), nausea and vomiting (placebo = 1 - 9%, all doses = 9 - 75%) and eating disorder (placebo = 2 - 6%, all doses = 5 - 16%) were most frequently reported. Dizziness (placebo = 4 - 13%, all doses = 11 - 38%) and agitation (placebo = 6 - 16%, all doses = 4 - 8%) were also reported.

Posatirelin. Four trials evaluated posatirelin in 931 subjects in a variety of mild to moderate dementia populations (AD, PDD, VaD) using a dose of 10 mg per day over 3 months duration.

Three of the four trials showed statistical significance for general cognitive function and quality of life/ADL (as measured by GBS subscales for these domains). The evidence remains

inconsistent for benefit in global assessment (evaluated in only one trial) and behavior/mood (mixed results). Caregiver burden and specific cognitive function were not evaluated in any trial.

Quality scores for reporting adverse events varied from 2 to 4. Withdrawal rates due to adverse events ranged from 0 - 3% in placebo and 0 - 4% in the treatment group. None of the studies tested for significant differences between groups. All studies reported the presence of agitation, and at least three studies reported arrhythmia, nausea/vomiting, headache, rash/skin disorder, and sleep disorder. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = 1 - 4%), 2) dizziness (placebo = not reported, all doses = 1%), 3) diarrhea (placebo = 2%, all doses = 2%), 4) agitation (placebo = 1 - 5%, all doses = 1 - 5%), and none reported eating disorder as an adverse event.

Rivastigmine. Six studies evaluated 2071 subjects and three of these studies were limited to AD patients only. Doses for rivastigmine varied from 1 to 12 mg, and treatment ranged from 14 to 26 weeks and only one study specified a community sample.

The evidence shows that general cognitive function improves with rivastigmine at a dose of 12 mg, but there is mixed results for efficacy at lower doses. Two trials also evaluated specific cognitive function but the results were not consistent within studies (between general and specific measures) and between studies for these domains. There is consistent evidence of benefit for the outcome of global assessment but the dosage at which this is significant varies highly between studies. In the domains of behavior/mood and quality of life/ADL, the findings were not statistically significant nor consistent; most of these analyses were not based on intention to treat analysis and lack of sufficient power cannot be ruled out. Caregiver burden outcomes were not evaluated by any trial.

Quality scores for reporting adverse events varied from 2 to 5. Withdrawal rates due to adverse events ranged from 4 - 11% in the placebo and 11 - 27% in the treatment group. Two trials demonstrated a dose response; however, one of these trials showed significant differences for nausea and vomiting only, and the other trial showed significant difference for all the adverse events reported. The majority of studies reported dizziness, nausea and vomiting, eating disorder/weight loss, and headache. It should be noted that one study allowed intentional prescribed anti-emetic drugs to increase the tolerance of subjects taking rivastigmine. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3 - 10%, all doses = 8 - 58%), 2) dizziness (placebo = 0 - 7%, all doses = 6 - 20 %), 3) diarrhea (placebo = 2 - 9%, all doses = 7 - 17%), 4) eating disorder (placebo = 4 - 8%, all doses = 4 - 19%), and 5) agitation was not reported.

Tacrine. Six studies[108,109,110,111,112,113] evaluated tacrine in 994 subjects predominately with mild to moderate AD at doses of 80 to 160 mg lasting either 12 - 13 or 3 - 36 weeks in duration. Two other studies[114,26] involving 425 patients were non-placebo controlled studies.

A single trial[108] was found to show benefit for general cognitive function with a small effect and this was based on a series of related publications. The five trials showing no benefit for general cognitive function comprised small sample sizes and much shorter study duration. Overall, the evidence for benefit for general cognitive function is limited to this single trial. There is evidence for benefit in global function from two of the three trials that evaluated this domain. Changes in behavior/mood, quality of life/ADL domains, specific cognitive function, and caregiver burden were all not significant, but lack of sufficient power cannot be ruled out.

The quality scores for reporting adverse events varied from 1 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0 - 12% for placebo and 0 - 55% in the treatment group. The higher rates of withdrawal were associated with higher doses. Elevated alanine transaminase (ALT) or hepatic abnormality (placebo = 4 - 13%, all doses tacrine = 7 - 67%) was reported in six studies, raising concerns for the potential for serious liver damage. None of these trials tested for differences between treatment and placebo with respect to adverse events. Five of the studies reported nausea and vomiting (placebo = 0 - 9%, all doses = 9 - 37%); gastrointestinal problems; dizziness (placebo = 0 - 16%, all doses = 4 - 14%) was also noted in several studies. Frequencies of other a priori symptoms of interest are as follows: 1) agitation (placebo = 5 - 12%, all doses = 5 - 9%), and 2) diarrhea (placebo = 0 - 13%, all doses = 4 - 18%). There is evidence for the potential for serious adverse events associated with liver function in six trials.

Velnacrine. Three studies evaluated the effects of velnacrine in 774 AD patients with a diagnosis of AD. The doses that were shown to effect significant changes were 75 mg twice daily and 225 mg daily in studies with a 15 and 24 week duration. Location of recruitment was not specified.

Statistically significant effects were observed for general cognitive function, and global assessment in the two studies with sample sizes over 300 subjects. Behavior/mood and caregiver burden showed some benefit in one trial[116] at the highest dose only. Quality of life/ADL was tested as a secondary outcome and showed mixed findings.

Quality scores for reporting adverse events were 3 for all studies. Withdrawal rates varied from 0 - 22% for the placebo group and 5 - 33% for the treatment group. None of the studies reported a dose response. None of the studies tested for statistical differences between the placebo and treatment groups. Two studies reported aberrant hematology and hepatic abnormality;[116,117] for these two studies the rates of occurrence were 2 - 21% for placebo, and 32 - 40% for all doses. All studies reported diarrhea and nausea and vomiting. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 0 - 4%, all doses = 3 - 8%), 2) dizziness (placebo = 3%, all doses = 0 - 8%), 3) diarrhea (placebo = 3%, all doses = 2 - 33%), 4) agitation (placebo = 4%, all doses = 1 - 4%), and 5) eating disorder (placebo = 1%, all doses 2 - 4%). The potential for serious liver effects was not well specified in these trials.

Summary of Non-cholinergic Neurotransmitter/Neuropeptide Modifying Agents

Haloperidol. Five studies evaluated the effect of haloperidol relative to placebo in a total of 622 subjects with mild to moderate disease and included AD patients[124,125,128] and mixed populations (MID/VaD/ PDD).[126,127] One trial[128] had only 15 patients, and one trial[124] lasted only three weeks. Two studies recruited subjects from institutions; one from the community and two did not specify.

Mixed results were observed for improvement in global assessment. In three of the trials there was benefit in the domain of behavior/mood which reached statistical significance. Two trials evaluated caregiver burden and found no statistically significant differences but lack of sufficient power cannot be ruled out. Few studies evaluated outcomes in quality of life/ADL. Haloperidol did not affect general cognitive function in two trials and was not evaluated in the other studies.

The quality scores for reporting adverse events varied from 1 to 5 and only three of five studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 5% to 17% for placebo and 17 – 33% in the treatment group. One trial[124] showed a dose-response effect but the study only lasted for three weeks. Three trials tested for differences between treatment and placebo with respect to extra pyramidal symptoms (placebo = 17 - 32%, all does = 34 - 97%), and two found statistically significant differences.[124,125] One study[125] found significant differences between groups for balance-related problems. Although reported by only two trials, the range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = not reported, and 2) dizziness (placebo = 24%, all doses = 21%). No frequencies were reported for agitation, diarrhea, or eating disorder.

Memantine. Three trials evaluated memantine in 1066 patients, primarily with VaD, with 10 or 20 mg doses lasting 12 or 28 weeks. Disease severity was moderate to severe in a single study[132] and mild to moderate in the remaining two studies[133,134]. One study included patients that were institutionalized, one from the community and the third did not specify.

There is consistent evidence of benefit for general cognitive function in the two studies that evaluated this domain. The findings for global assessment are mixed. The sole trial that evaluated mixed dementia populations (including some VaD) with moderate to severe dementia found significant differences for global function, behavior/mood, and quality of life/ADL outcomes, but did not evaluate general cognitive function. It should be noted that this trial with mixed populations used half the dose of memantine for half the study duration in patients with greater disease severity, and had approximately half the sample size of the other two trials evaluated in this systematic review. Despite a lower dose, a smaller number of more severely affected patients, and a shorter duration, a statistically significant difference was found.

The quality scores for reporting adverse events varied from 3 to 4. Only two of three studies reported withdrawal rates; the proportion of subjects withdrawing due to adverse events ranged from 7% to 13% for placebo and 9 - 12% in the treatment group. A single trial tested for differences between treatment and placebo, and none of the comparisons were significant. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 3%, all doses = 5%), 2) dizziness (placebo = 3 - 8%, all doses = 6 - 11%), 3) diarrhea (placebo = 4%, all doses = 4%), 4) agitation (placebo = 7 - 8%, all doses = 4 - 5%), and none reported eating disorder as an adverse event.

Selegiline. Six trials[135,136,249,138,139,140] evaluated selegiline in 733 patients with AD, PDD, and DAT with 10 mg per day and a study duration of 60 days or 2 years. Only one study reported that patients were from institutional settings.

All but one trial that evaluated general cognition showed no statistically significant changes. A single trial found statistical improvements in specific cognitive tests (Sternberg Memory tests); this trial also showed statistically significant improvements in global assessment and behavior/mood. Only this trial, which had the highest quality score (7), showed consistently positive findings across domains tested. Three of the five trials that evaluated part or all of these domains had very small sample sizes and were likely underpowered, possibly accounting for the inconsistent findings. There is some evidence that selegiline and selegiline combined with vitamin E, increases the time to important functional decline milestones; this is based on a single study.

The quality scores for reporting adverse events varied from 0 to 3. The proportion of subjects withdrawing due to adverse events ranged from 0 - 4% for placebo and 0 - 9% in the treatment group. Only one trial[135] tested for differences between the treatment and placebo groups and showed that balance and falls were significantly different (worse) between groups (22% for the group with selegiline combined with vitamin E versus 5% in the placebo). When adjusted for multiple comparisons, these were no longer significant. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 2%, all doses = 0%), 2) dizziness (placebo = 2 - 20%, all doses = 0 - 30%), and 3) agitation (placebo = 4 - 16%, all doses = 4 - 23%); no trial reported diarrhea or eating disorder as an adverse event.

Summary of Other Pharmacological Agents

Cerebrolysin. Six studies evaluated the effect of cerebrolysin in a total of 819 subjects. All but one of the trials[171] included only AD patients with mild to moderate disease. All of the studies used the same dose of cerebrolysin, 30 ml per day for 5 days per week for 4 to 24 weeks. Location of recruitment was not specified.

Cerebrolysin showed a statistically significant effect on cognition in four out of five studies. Although, a pooled estimate for the ADAS-cog was calculated, the model was positive for heterogeneity and the overall estimate was not significant. The results for specific cognitive tests for the three trials that evaluated this domain were inconsistent. Global assessment measures

showed a significant effect in five of the trials. This model was also positive for heterogeneity but significant for an overall effect. Two out of three studies showed an effect for behavior/mood, and none of the six studies showed an effect on quality of life/ADL. No study measured caregiver burden.

Two of the six trials scored 5 out of 5 on our quality scale for rating adverse events, yet they did not report any adverse events. Two studies scored 4, and the other two trials scored 3 and 2. All the studies with scores equals to 4 or less tested for statistical differences in adverse events between placebo and treatment groups. Withdrawals due to adverse events were not reported in one study[170] and were 1% in two studies[173,168] and none withdrew in three studies.[169,172,173] One study reported significant differences between treatment and control group[173] for weight change, anxiety, and headache. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 10 - 24%, all doses = 3 - 21%), 2) dizziness (placebo = 0 - 12, all doses = 1 - 8%), and 3) agitation (placebo = 1%, all doses = 0%), and none reported diarrhea or eating disorder as an adverse event.

Estrogen. Five studies evaluated estrogens for dementia in 247 patients with primarily mild to moderate AD, with the exception of one study[178] that included moderate to severe dementia patients who were all institutionalized. One of the studies with AD patients provided 0.10 mg per day[174] by skin patch for 8 weeks and the others used 1.25 mg per day for 12 to 52 weeks.[177] The study including severe subjects used 2.5 mg per day for 4 weeks.[178]

Three trials evaluated general cognitive function and all showed non-significant findings; two of these trials lacked sufficient power for the ADAS-cog. Similarly, two trials evaluated specific cognitive function but results were mixed. Most of the outcomes evaluated in the domains of global assessment, behavior/mood, and quality of life/ADL were secondary outcomes and none showed significance; lack of power could be a factor in these trials.

One of the five trials scored 5 out of 5 on our quality scale for rating adverse events, and surprisingly, this same trial did not report any adverse event. Withdrawal rates due to adverse events ranged from 0 - 5% for placebo and 0 -14% for the treatment group. The most frequently reported adverse event was vaginal bleeding and a single trial reported a significant difference between placebo and treatment group for this symptom. It was not clear from the descriptions provided in the study if they had ascertained whether vaginal bleeding was present prior to the trial commencement. Nausea was the single a priori symptom of interest that was reported and by a single trial; frequencies varied from 0% for the placebo group and 4% for the treatment group.

Ginkgo biloba. Three trials evaluated Ginkgo biloba, 120 to 240 mg per day for 3 to 12 months, in a total of 563 subjects with mixed dementias of mild to moderate severity.

The largest trial[179] had the longest treatment interval but the lowest daily dosage and reported a significant effect for general cognitive function but had mixed findings for global assessment.

A second large trial[181] found positive changes for neuropsychological tests, global assessment, and behavior outcomes with double the dosage of the previously described trial and half the treatment interval. In this same RCT, clinical efficacy was assessed by using a responder analysis, with therapy response being defined as response in at least two of the three variables: CGI (global function), SKT (special cognitive function), and NAB (ADL). A single trial evaluated behavior/mood and was not significant. No trial evaluated caregiver burden or quality of life/ADL.

All three trials scored 3 or greater on the quality scale for rating adverse events. Two studies had no withdrawals due to adverse events, and one trial had a withdrawal rate of 6% for both placebo and treatment groups. Two studies did not report any adverse event. One study reported a statistically significant difference between the treatment and the placebo group for skin disorders. The same study reported gastrointestinal and headache adverse effects, but did not test for statistical differences between the placebo and the treatment group. None of the trials reported the presence of the a priori symptoms of interest.

Idebenone. Four studies[185,183,182,184] evaluated the drug idebenone in 1153 subjects of mixed dementia populations of mild to moderate severity; one of these trials[26] evaluated idebenone relative to tacrine. Doses varied from 30 mg per day to 360 mg per day, and the treatment interval ranged from 90 days to 60 weeks.

There was evidence of benefit for general cognitive function and global assessment. Several studies evaluated behavior/mood and quality of life/ADL and these outcomes were found to be significantly different. None of the trials evaluated caregiver burden.

Quality scores for reporting adverse events varied from 1 to 5. Rates of withdrawal due to adverse events varied from 0 - 5% for the placebo group and 0 - 5% in the treatment group; a single trial[183] did not report withdrawal rates. Two trials[183,185] tested for statistical differences between groups and found no differences. Although no clear pattern emerges, three studies identified at least one balance-related adverse event most consistently reported across studies. The range of frequencies of the a priori symptoms of interest are as follows: 1) nausea (placebo = 2%, all doses = 2 - 11%), 2) dizziness (placebo = not reported, all doses = 2%), and 3) not reported for diarrhea, agitation, or eating disorder as an adverse event.

Oxiracetam. Five studies[186,187,188,189,190] evaluated oxiracetam in 554 subjects with different dementia syndromes of mild to moderate severity. All analyses were observed cases and not ITT. All studies used 1600 mg daily, with one exception[189] where the dose ranged between 1600 - 2400 mg per day. The treatment interval ranged from 90 days to 26 weeks.

All outcomes shown to be positive for this drug were based on observed case evaluation. The two trials that evaluate general cognitive function showed benefit. The findings for specific cognitive function were mixed. A single trial evaluated global assessment and showed statistically significant change. Behavior/mood, and quality of life/ADL outcomes showed mixed results. No study evaluated caregiver burden.

The quality scores for reporting adverse events varied from 2 to 5. The proportion of withdrawals due to adverse events varied form 0 - 9% for the placebo group and 0 - 6% for the treatment group. No clear pattern for adverse events is evident, but three of the five studies reported gastrointestinal related problems, primarily associated with abdominal pain. Although, only single trials evaluated the range of frequencies of the a priori symptoms of interest are as follows: 1) dizziness (placebo = not reported, all doses = 11%), and 2) agitation (placebo = 1%, all doses = not reported); no trial reported nausea, eating disorder, or diarrhea as an adverse event.

Pentoxifylline. Three placebo-controlled studies[193,192,191] evaluated pentoxifylline and one study[194] compared pentoxifylline to sulodexide, with a total of 482 subjects with predominately MID. The total dose administered in all studies was 1200 mg per day but varied from 400 mg three times per day to 1200 mg once per day. The treatment intervals ranged from 12 to 36 weeks.

All three placebo trials showed non-significant findings for any primary outcome evaluated on all subjects in the study. It should be noted that two of these trials had very small sample sizes (n = 38, n =28) that were evaluated in the OC analyses; this suggests that the trials lacked sufficient power to evaluate multiple outcomes. The remaining trial had a large sample size (n = 289) and employed an ITT analysis; all primary outcomes evaluated were not significant.

The quality scores for reporting adverse events were generally low, varying from 1 to 3. Withdrawal rates due to adverse events varied from 0 - 25% in the placebo group and 0 – 22% in the treatment group. The two studies that reported adverse events indicated the presence of gastrointestinal disturbances, including abdominal pain or nausea and vomiting (placebo = 7% and all doses = 14%). None of the trials reported dizziness, agitation, eating disorder or diarrhea.

Propentofylline. Four trials[197,196,250,198] using propentofylline in 510 patients with AD and VaD were included. A dose of 900 mg per day was consistent across all studies, and the treatment duration ranged from 3 to 12 months.

The two studies with small sample sizes (n = 30) showed no significant results for any outcome evaluated but lack of power cannot be ruled out. There were two trials that found benefit in general cognitive function based on the MMSE. The results for specific cognitive function as measured by the DSST were mixed, as were those for global assessment. Behavior/ mood outcomes were evaluated by a single trial[195] and shown to be significant; this same trial evaluated quality of life/ADL and showed no significant difference. No trial evaluated caregiver burden.

The quality scores for reporting adverse events varied from 1 to 4. The percentage of withdrawals varied from 0 – 13% for the placebo group and 0 – 12% for the treatment group. None of the trials tested for differences between groups. Three of the trials[195,197,198] reported gastrointestinal events that included abdominal pain, constipation, and nausea and vomiting (placebo = 2%, all doses = 7%). Dizziness (placebo = 3 - 5%, all doses = 1 - 6%) was the only other a priori symptom of interest.

Methodological Issues and Limitations in Assessing Efficacy of Dementia Agents

Definition of clinically significant or meaningful difference. The stance undertaken in this review has been cautious with regards to interpreting "clinically significant" differences within and across studies. This systematic review has highlighted some of the concerns expressed in the literature on pharmacological efficacy research in dementia. Ultimately, clinical significance is a complex issue, and its definition can vary across individuals and groups of individuals. Wherever possible, attempts were made to identify the magnitude of differences in the studies and the limitations of the data from some of these primary studies.

In drug development programs, an ordered series of trials are undertaken: dose tolerance (phase I), dose finding (phase II), dose efficacy (Phase III), and post-marketing (phase IV). However, due to the pressures on pharmaceutical companies to develop drugs quickly and cost-efficiently, a drug may move into the next phase of development before evidence of the previous phase is known.[251] Even when phase III trials are carried out in an adequate manner, the interpretation of the efficacy results is hampered by multiple p-values, disagreement over the need for multiplicity corrections, and the potential for conflicting evidence from trials of different sizes.[251] Some of these difficulties can be minimized by measuring a single primary efficacy variable at one point in time and using a p-value of less than 0.025 (one-tailed, as the aim is for the statistical test to determine if the drug performs better than the placebo or low dose).[252] This presumes that good dose-response data exist, identifying a single dose level as the best candidate for further evaluation. Lastly, interpreting differences on the basis of statistical significance has long been recognized as problematic. Clinically meaningful change reflects a different level of "significance" and often requires consensus among experts within the field for these criteria.

Issues of diagnosis and severity. Three methodological issues related to population classifications have limited the inferences that can be garnered from this systematic review. The first issue concerns the classification models used for diagnosing dementia; they are not interchangeable among the various types of dementia and the "pre-clinical" forms of slight cognitive impairment. Moreover, there are still concerns about the accuracy of these criteria. For example, in the American Academy of Neurology's (AAN) recent evidence-based review of dementia case definitions, none met the AAN's highest evidence standard. A clinical diagnosis of AD is only 28% specific after age 79 years. Similarly, no dementia screening measure is accurate enough to be recommended by the American Society of Internal Medicine.[253] The AAN specifically faulted the emphasis on memory function in dementia case definitions.[254] Yet tests like the ADAS-cog emphasize memory loss at the expense of other cognitive domains, especially executive control function,[31] and many anti-dementia treatment strategies target neurotransmitters and structures (like acetylcholine and the hippocampus), which mediate memory test performance.

A second consideration in defining populations of dementia patients concerns determination of severity level. The MMSE, although frequently used, may not best capture severity. Many studies were observed to define the severity (mild, moderate, severe) of dementia populations based on the MMSE. For example, a range from 10 to 26 has been used to define a mild to moderate severity level.[50] Given that the maximum and minimum instrument scores are 0 and 30, this suggests that the extreme ends of the spectrum, particularly the "severe" end (i.e. <10), represent a very narrow proportion of patients. These two broad categories (mild to moderate and severe) may not actually reflect the cognitive and functional differences in a clinically meaningful manner. The MMSE does not address issues of executive control function (as required by the DSM-IV dementia case definition), which is known to be a good predictor of functional status. From a research perspective, a better classification reflecting disease severity may be an important factor for stratification and determining the efficacy of pharmacological interventions.

Outcome issues. The studies evaluated in our review used 181 different outcomes across seven domains. This raises the issue of which of these outcomes are considered by clinicians to be most "clinically relevant". Let us assume that the most clinically relevant outcomes for all the drug interventions for dementia are the ADAS-cog and the MMSE because they are very commonly reported in studies.

In this dementia review, numerous studies did not measure outcomes evaluating cognition, as the intended effect of the drug was not always in the domain of cognition (e.g. neuroleptics for behavior control). Moreover, a large number of the studies that used important clinical cognition outcomes, such as the MMSE, did so only to establish baseline severity, or they used it as a secondary outcome. This presents us with some difficulty in the consistency of reporting on this limited set of "clinically relevant" outcomes. There is also the issue of which domain (i.e. cognitive function versus ADL versus behavior) is the most clinically relevant. The FDA guidelines suggest cognition and global assessment; the EMEA guidelines suggest the addition of an ADL or quality of life/ADL measure as being most clinically relevant. Thus, some consensus work needs to be done among experts in the field to determine the most clinically relevant outcomes and domains. For example, the choice of most clinically relevant outcome may depend upon type and stage of dementia (e.g. for mild AD, neuropsychological outcomes may be are the most important domain while for severe AD, behavior may be the most relevant outcome), which may challenge the achievement of consensus.

To our knowledge, no specific set of outcomes that define "clinical relevance" applies to all the drug interventions we evaluated. The FDA has recommended that "dual efficacy" of dementia drug interventions be established by significant change in both a psychological measure and a global change measure. The outcomes measuring these attributes within these two domains were not specified. However, there was a general trend for using the outcomes ADAS-cog and CIBIC+ to capture these two attributes when evaluating drugs for AD populations.

Ideally, all outcomes should have demonstrated acceptable psychometric properties, such as reliability, validity (construct), and responsiveness. We did not a priori evaluate the properties of outcomes reported in the eligible studies. In some cases, these outcomes were developed in non-

English languages but the original study was reported in English. In considering the psychometric properties of some of the outcome instruments used, the attribute of responsiveness is critical, and some have suggested that this has not been adequately evaluated in many outcome measures.[33,30,255]

We might envision a clinically relevant pharmacological treatment as one that has made a real difference, where the change is both relevant and important to the patient or to clinicians. This fundamentally shows the difference between clinically significant (relevant and important) versus statistically significant (associated with probabilities), where the latter determines that the results are not due to chance. Moreover, a clinically important change will vary depending on whether importance is defined from the patient or clinician perspective.

Five different levels of responsiveness (ability to detect change) of outcome measures have been defined:[256] 1) Minimal change potentially detectable (essentially an attribute of the scoring method of the outcome), 2) Minimal change actually detectable beyond measurement error of the instrument (also defined as Minimum Detectable Change (MDI) or Reliability Change Index (RCI), which includes the Standard Error of the Measurement (SEM)), 3) Observed change (often reported as the standardized response mean (SRM) or effect size (ES). 4) Observed change in those estimated to have improved; the key to understanding change in this instance is that an external standard is used to determine whom has improved (often reported as comparison between groups that have improved versus those who have not; the improved group can be defined by either patient and/or clinician or a combination), and 5) Observed change in those estimated to have important improvement (often reported as the minimal clinically important difference and can be determined by the patient or clinician, or a combination of both).

Consider the ADAS-cog and the CIBIC+: The minimal change detectable is 1/70 = 0.0143 for the ADAS-cog and 1/7 = 0.143 for the CIBIC+, suggesting that the ADAS-cog can detect smaller increments of change relative to the CIBIC+. Thus different instruments have differing sensitivities to detecting change. There is scant literature on the responsiveness of outcome measures as defined in number 4 above, observed change in those that have improved, or as in number 5 above, observed change in those estimated to have important improvement. Thus, we have identified a significant gap in the literature with regard to estimating clinically important changes. Much greater consideration of issues of responsiveness should be given in future research in efficacy trials of pharmacological agents. Greater understanding of clinically important change suggests that some of our current judgments of efficacy are limited as these important differences need to be established.

Analysis issues. The inability to estimate the power of a study to detect a difference presented significant limitations in interpreting those studies that showed no significant differences. Similarly, the lack of sufficient data for estimating effect size limited the ability to show the magnitude of the change. It is recommended that future trials evaluating the efficacy of pharmacological agents adhere to the CONSORT guidelines in order to provide sufficient data to estimate power and effect size for all relevant outcomes.

Although the difficulty of maintaining adherence to long-term drug interventions among dementia patients is acknowledged, the ITT analysis should continue to be the analysis of choice in trials. Ideally, both ITT and OC analyses should be presented. If both suggested the same conclusion, confidence in the study results would be increased.

Problems with funding/ sponsorship exclusively from drug companies. The sponsorship of studies by for-profit organizations has led to bias towards the publishing of positive results.[257] These findings suggest that there are powerful disincentives for pharmaceutical companies to publish negative trials. This is contrary to what academic-based, non-industry funded trials show, where the publication of negative trials are more likely.

A recent evaluation of FDA databases for antidepressant drugs[258] in the US, suggested that less than half of antidepressant trials were negative, which does not correspond to the published literature. In this systematic review, no attempts were made to contact industry for unpublished trials, which introduces the possibility of a bias associated with not reporting negative trials. Additionally, we did not contact authors who did not specify funding sources for their studies. Future research on the efficacy of pharmacological agents to treat dementia should indicate all sources of funding and who undertook the study analyses.

Adverse events. In this systematic review, the type and frequency of adverse events associated with the use of a drug intervention were scrutinized and reported to a greater extent than previous reviews of anti-dementia drugs. Attempts were made to weigh the potential for harm against the benefits when determining the efficacy of pharmacological interventions. Empirical evidence across diverse medical fields indicates that reporting of safety information (including milder adverse events) receives much less attention than the positive efficacy outcomes.[35] Thus, it was recognized that an evaluation of the benefits of anti-dementia pharmacological agents alone may present a biased view of the efficacy of the intervention.

The ability to capture and evaluate adverse events proved to be difficult for several reasons. For example, although metrifonate had good evidence of positive effects on cognitive function, it was banned from use due to the risk of respiratory paralysis. The description of serious adverse events in the trials we evaluated did not capture this type of event, nor did different studies identify "serious events" in a consistent manner. This points to several fundamental limitations. The first of these relates to the limitation associated with the RCT design itself, which is less likely than the longitudinal cohort study designs to capture serious adverse events that are rare. Secondly, many trials were of relatively short duration and captured "idealized" dementia populations. Many of these trials were from pre-marketing studies contracted by pharmaceutical companies in carefully controlled research settings. Dementia patients seen in practice may have more complex medical illnesses and are at greater risk for potential side effects. In addition, drugs used in "polypharmacy" have even greater potential for pharmacological interactions. Furthermore, practitioners may prescribe these pharmacological agents for wider indications than originally intended, or may not refrain from withholding the drug from certain high-risk subgroups, leading to increased risk of adverse events. Thus, published rates of adverse events in well-controlled trials may underestimate true rates seen in practice.

Thirdly, by their nature, some adverse events are not easily anticipated, and therefore are not screened for in some trials. Adverse events may be hard to predict or anticipate but can be captured only if a trial protocol was designed to measure these events. This problem is compounded by the lack of consistency in what constitutes "serious" events or how the severity of the typical events is rated. A limited number of standardized instruments exist to capture these events reliably, but the overwhelming majority of studies in this systematic review did not use these instruments. Furthermore, capturing information from individuals with cognitive decline can create problems; the validity of the self-report instrument, even if completed by the caregiver, can be problematic. More research on the reliable collection of adverse events in dementia populations (with compromised cognition) may be required.

A fourth consideration concerns the issue of off-label use of pharmacological agents. Given that only four drugs are currently approved by the FDA for the treatment of dementia, the other 97 interventions evaluated in this review are classified as "off label use" but many are not approved by the FDA and not, therefore, available. For some of these off-label medications the potential mechanism of action on the disease process has not been fully established (if even considered), yet they have been applied to dementia populations. This off-label use of pharmacological agents may present further difficulties in evaluating adverse events.

Question 2: Does pharmacotherapy delay cognitive deterioration or delay disease onset of dementia syndromes?

Summary of Systematic Review Results

Few studies evaluated delay of onset or delay in disease progression. A definite gap for evaluating disease onset (as defined by the selection of populations at risk such as MCI populations) has been identified in this review.

Conversely, the need for good evaluation of disease progression in trials was also identified. In general, few studies evaluated subjects in more severe state of the disease. This suggests that a bias exists towards evaluating mild to moderate disease in the trials eligible in this systematic review. This in turn reflects the underlying assumption that the less severe groups are most likely to benefit from drug trials. Since so few studies have evaluated the more severe groups, this assumption may require some empirical justification in future research. Those studies that evaluated severe patients showed some potential for benefit. Future research in this area may require some consensus regarding the classification of severity levels.

Three studies evaluating cerebrolysin,[168] selegiline and vitamin E,[135] and donepezil[61] have shown significant effects in delaying disease progress in mild to moderate[61,168] and moderately severe disease in patients with AD. This delay in progress was expressed in terms of delay in days to primary event[135,61] or statistical differences between placebo at a specified time interval.[168] Although these two trials coincidentally evaluated dementia patients over the longest time interval, it did not withdraw the drug at the end of the study. Theoretically, conclusive evidence of disease delay would be demonstrated if the treatment groups did not return to the level of the placebo. Thus, distinguishing between symptomatic and disease modifying effects is

not possible unless the drug is withdrawn and the treatment group(s) are observed for these changes.

When studies attempted to evaluate disease progression, long-term (1 year or greater) trials continued in an "open-label fashion", where blinding was no longer maintained. This limits the confidence that bias did not affect the subsequent changes in the outcomes. It was observed that increasing levels of dropout (for a variety of reasons) also plagued these open-label phases of evaluation. From a practical perspective, maintaining adherence in longer-term trials in dementia patients are challenging,[19] particularly for those in the placebo arm or for those interventions that have a high proportion of adverse events.

A number of trial designs have been proposed to capture delay in disease progression versus symptomatic treatment. Some of these trial designs include withdrawal of treatment, active-extension, randomized withdrawal, randomized start, and staggered start designs.[235,236,19,21] One important aspect of these designs is the selection of an adequate washout period or an adequate follow-up period. In addition, longer evaluation with survival analyses may be a good strategy to evaluate delay in disease progress for some drugs. One advantage of this design is the selection of clinically relevant milestones (functional changes over time), which was utilized in two studies [63,136]; the selection of such events may merit greater consideration in future trials evaluating delay. A more critical analysis of the staggered/start/stagger withdrawal design in comparison to the survival analysis would be helpful. Also, one could provide a more extensive analysis of the data on propentofylline and vitamin E,[136] which represent the most extensive efforts to use the stagger/start/stagger withdrawal and survivor analysis approaches, respectively. Future research seeking to establish efficacy should clearly specify if symptomatic treatment or delay in progression is the therapeutic aim. This is important for determining specifically if efficacy is considered with respect to these two aims. Accordingly, a design that can establish this aim should be selected.

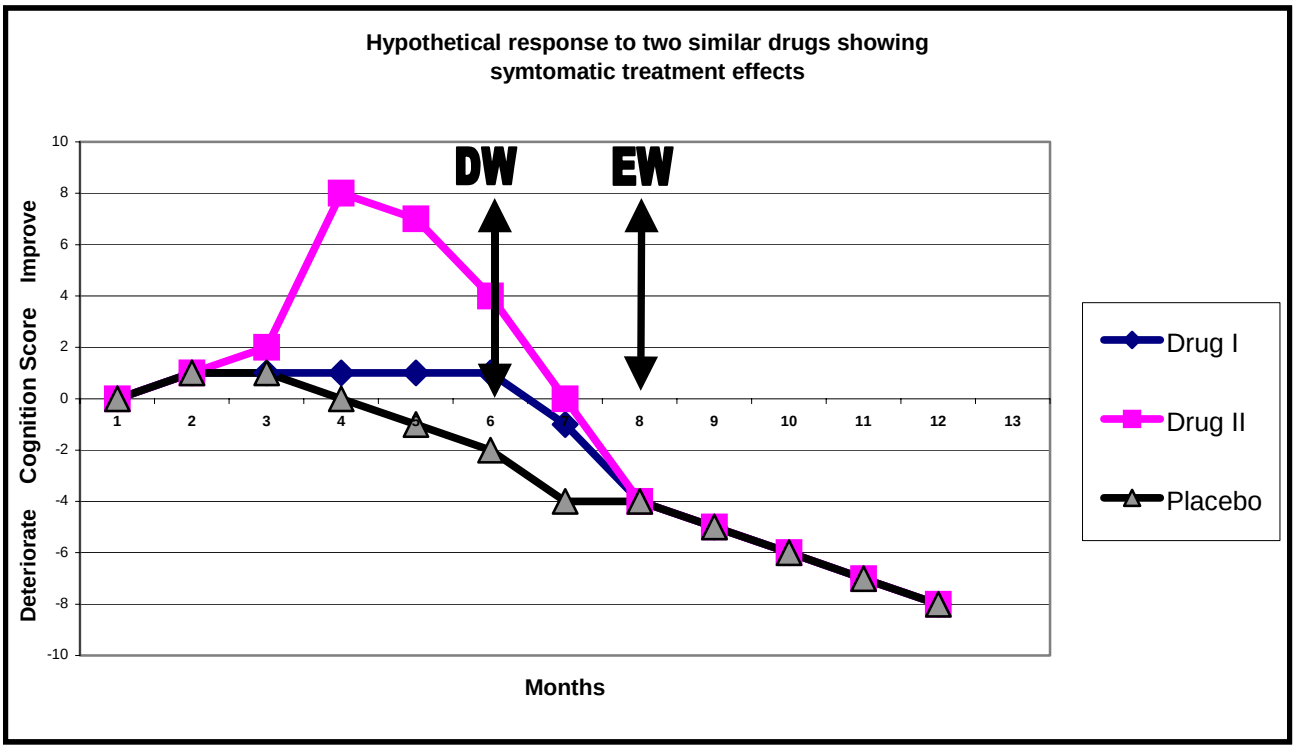
Methodological Issues

Determining symptomatic treatment versus affecting delay in disease progress. Figure 31 depicts hypothetical responses of dementia patients to two similar pharmacological interventions relative to placebo. In this example, the placebo group changes over time were modeled according to the natural history of AD as described by Stern et al. (1994)[29]; the progressive decline of the AD subjects may not be representative of all dementia types. For simplicity's sake, the decline is assumed to be linear, although the literature has suggested the rate of decline varies between the different types of dementia and within each of these groups as a function of the disease severity.[21,259] The two drugs depicted in Figure 31 are similar in that they have the identical titration (approximately 8 weeks) and washout periods. In this hypothetical scenario, the drugs are both withdrawn at 6 months (DW) and the washout periods have ended at 8 months. Within the active treatment period (first 6 months), the response to Drug I depicts the maintenance or stabilization of cognition function relative to the placebo, whereas the response to Drug II suggests improvement (or restoration) of cognition for a short period. However, the rapid decline of cognition scores within the two treatment groups to the level of placebo at 8 months (end of the washout period (EW)) suggests that the treatment effect was symptomatic relief. Upon withdrawal for subjects exposed to either Drug I (maintenance or stabilization) or

Drug II (improvement relative to baseline and placebo), the cognition scores declined to the same rate of placebo, and thus no delays in disease progression were demonstrated.

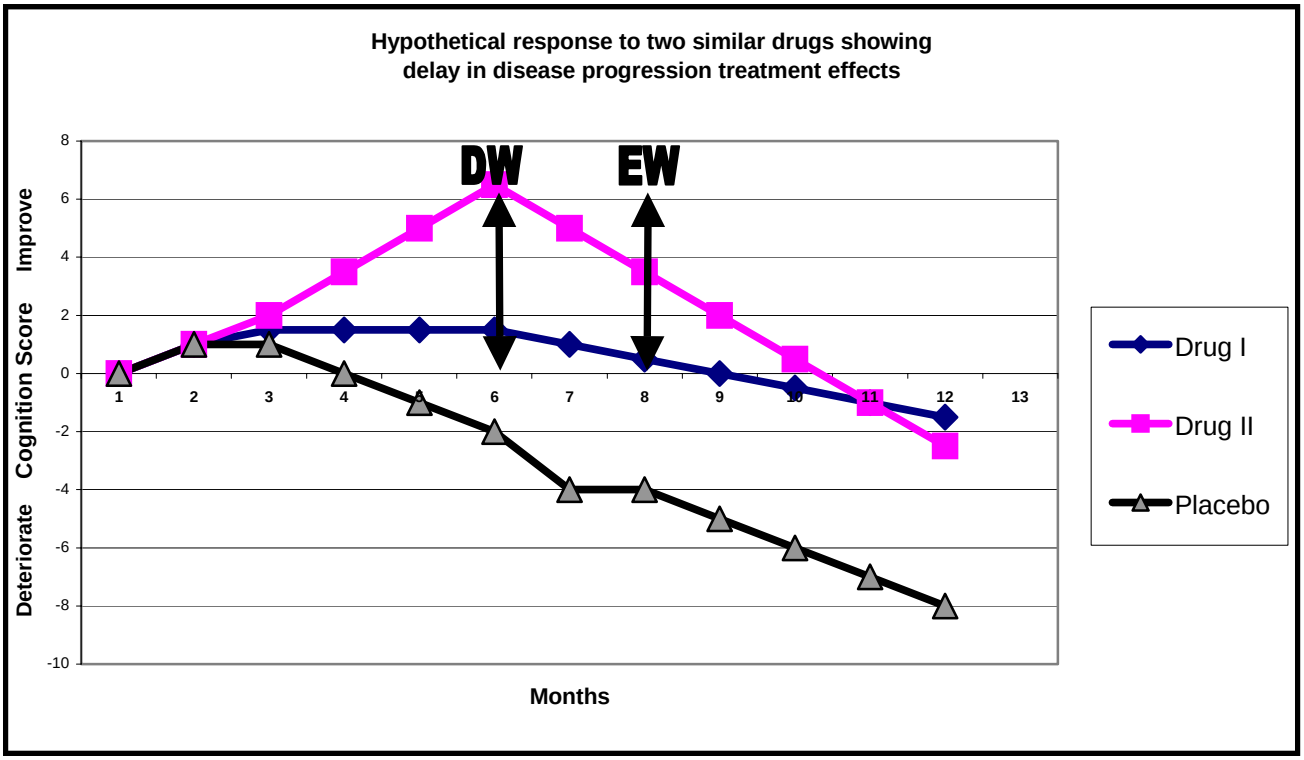
In contrast, Figure 32 shows a delayed rate of decline relative to placebo after the withdrawal of the pharmacological interventions. The response depicted for the treatment group exposed to Drug I shows that cognitive function is maintained until the drug is withdrawn (DW) and then the rate of decline is slower relative to the placebo (different slope of change) following the washout period. The response of the treatment group exposed to Drug II would suggest that cognition is improved for an interval (relative to baseline and placebo); when the drug is withdrawn, the rate of decline in cognitive function approximates that of the placebo group but is offset by approximately 6 months. Comparison of the slopes of the decline of cognition (Figure 32) would indicate a greater rate of decline for Drug II relative to Drug I, but both exemplify delay in progression of the disease effects. Theoretically, the treatment group rates of decline will never meet the decline rate of the placebo group when true disease modification has been effected by the pharmacological agent.

Figure 31. Delay of symptomatic treatment effects.



DW = Drug Withdrawn; EW = End of Washout

Figure 32. Delay in disease progression treatment effects.



DW = Drug Withdrawn; EW = End of Washout

In these two Figures (31, 32), the responses depicted have been idealized to clearly show the differences between symptomatic treatments versus disease modifying treatments. Additionally, two examples of the rate of decline as a characteristic of delay in disease progress have been explicated. However, in practical terms the most effective time interval for bringing about meaningful change in cognition (or other important outcomes), and the best time period to observe whether or not the effect is maintained (or lost), is not known. The difficulty in estimating these ideal time intervals is further compounded when the uncertainty of the rate of cognitive change (or decline) is considered.[21] It is likely that treatment effects may not be equal across all stages of the disease (mild, moderate, severe) or between the various types of dementia diagnoses.

The evidence provided in dementia trials to demonstrate the three broad therapeutic aims of pharmacological interventions has been expressed in a variety of comparisons. Ideally the changes due to the pharmacological intervention would be expressed in terms of differences between the treatment and placebo groups. Surprisingly, many trials have reported statistical significance between baseline and endpoint of the treatment group(s) as evidence of a therapeutic effect. Change has been described as "improvement" relative to the baseline for either of the treatment or control groups. Although, it is unlikely that AD subjects would ever improve spontaneously relative to baseline, it may be possible in some dementias. Additionally, the magnitude of the "improvement" is dependent on the time interval for which the differences

were estimated. Consider Drug II in Figure 31 at the 4- and 6-month intervals; clearly, the magnitude of the difference is greatest at 4 months. Similarly, the evidence for "stabilization" or estimates for "delay in progression" was dependent on the interval used for evaluation.

Question 3: Are certain drugs, including alternative medicines (including non-pharmaceutical) more effective than others?

Summary of Systematic Review Results

What may be most relevant to clinicians are head to head comparisons of the cholinergic modifying neurotransmitter pharmacological agents, particularly those currently approved for the treatment of dementia (tacrine, rivastigmine, galantamine, donepezil) in the United States. The evidence for each of these drugs has been extensively detailed, and the relative merits and handicaps of each were outlined in chapter 3. Relative effectiveness as demonstrated by effect sizes for the ADAS-cog and the CIBIC were also shown in chapter 3. Although, the psychometric properties of these two outcomes are well accepted, comparison across the populations in these pooled estimates may not lend themselves to direct comparison across these four different specific drugs. Thus, inferences about the relative effectiveness of these four medications specific for the treatment of dementia should be made cautiously as head to head comparisons were not undertaken.

Relative efficacy must be evaluated in direct comparison trials

From a methodological perspective, addressing the question of being "more effective" requires head to head comparisons of pharmacological interventions.

An evaluation of the trials that undertook direct head to head comparison of two distinct pharmacological agents was limited because only seven trials were identified. Although, these trials may have shown some relative benefit of one drug versus another, the clinical relevance of these particular agents is limited as none of the drugs currently approved by the FDA specifically for the treatment of dementia is represented in these eligible studies. Moreover, these studies are essentially limited to single trials and are not sufficiently strong to base recommendations on the relative effectiveness of drugs. Head to head comparison studies are beginning to appear in abstract form only and a significant gap in the literature has been identified.

Question 4: Do certain patient populations benefit more from pharmacotherapy than others?

Summary of Systematic Review Results

In general, very few trials examined the efficacy of dementia drugs across different populations or population characteristics. From the 13 studies that reported stratified analyses, eight different variables were identified, which included age, gender, APOE genotype, disease type, disease severity (as determined by MMSE/ ADAS-cog threshold levels), treatment center, care dependence, and presence of depression. Additionally, three trials were identified that evaluated efficacy in 1) patients with Down's syndrome and dementia, 2) different ethnicities as a function of treatment center in a multicenter trial, and 3) depressed patients. Given the relatively small number of trials evaluating these variables within different populations and different pharmacological interventions, the findings of this review are limited with respect to these patient variables. These reflect merely what has been reported in the literature rather than variables of importance with respect to efficacy of pharmacological therapies. A significant gap in the literature has been identified.

Representativeness of populations in the drug trials

The study population characteristics were detailed for the trials evaluated. A recent study,[22] suggests that many "real world" dementia patients in Ontario would not have met the eligibility criteria for participation in several of the cholinesterase inhibitor studies. This study highlights an important limitation of the pharmacological literature in that dementia patients recruited are not representative of the general dementia population. Additionally, clinicians and researchers should note that when a when a drug is approved for use, it is for a specific indication and a specific patient population. Evidence for one type of patient population may not necessarily be applied to another population. This is critical information to have when establishing clinical practice guidelines.

Question 5: What is the evidence-base for the treatment of vascular dementia?

Summary of Systematic Review Results

A total of 20 pharmacological interventions in 29 studies[211,220,238,171,200,199,146,68,181,184,133,134,132,161,89,91,93,247,187,191,192,194,193,100,98,196,195,245,217] were applied specifically to VaD classified dementias. The majority of these pharmacological interventions (n = 14) were represented by single trials, these interventions included ateroid, buflomedil, cerebrolysin, sulphomucopolysaccharides (CDP choline), citalopram, donepezil, Ginkgo biloba, idebenone, minaprine, nimodipine, oxiracetam, 5-THF (trazodone), vincamine, and xantinolnicotinate. Six interventions had more than a single trial, and these included Choto-

san (n = 2), memantine (n = 3), nicergoline(n = 2), pentoxifylline (n = 4), posatirelin (n = 2), and propentofylline (n = 2). In general, when the drug interventions were shown to be effective, it was in the domains of cognitive function (both general and specific) and global assessment. Other domains were less frequently evaluated. Several trials attempted to test for differences between VaD groups and other dementia types.

Diagnosis Classification of VaD

Erkinjuntti et al (1997)[1] compared six commonly used classification schemes (DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10 and the CAMDEX) and demonstrated that the prevalence of dementia can differ by a factor of 10 depending on the diagnostic criteria used. Two other studies have demonstrated that the prevalence of VaD varies with the classification system; therefore these criteria for diagnosis are not interchangeable.[10,11]

There is controversy about the validity of the clinical classification of VaD, as autopsy confirmation often does not substantiate the clinical diagnosis.[12,13] The majority of dementias were actually AD with co-existing VaD and PDD lesions.[14] In contrast, the clinical accuracy of AD diagnosis is relatively high.[7] Future research in vascular dementia should attempt to better distinguish this subgroup.

Determining Clinical Relevance

With rare exceptions, dementias are inevitably progressive and eventually lead to severe cognitive deficits, functional impairment, and often behavioral problems, unless death supervenes from intercurrent disease. The trajectories, sequence of clinical features, and burden on caregivers vary depending upon the type of dementia. For example, cognitive decline typically precedes functional impairment and behavioral disturbances in AD, while behavior and/or language problems typically announce the onset of frontotemporal degeneration.

Physicians and other health care practitioners have numerous roles in the management of individuals with dementia. These include identification, assessment and staging, classification, and prognostication, in addition to treatment of the individual and caregiver and planning for future disabilities (e.g. arranging alternatives to driving, assigning power of attorney and compiling living wills/advance directives).

Given these multiple tasks, how is the treating physician to interpret the results of therapeutic trials, which mostly deal with the pharmacological treatment of individuals with predominantly one type of dementia (AD) in the mild to moderate stages?

The traditional view of most physicians is that treatment success is measured by reversal of a disease, which is not a realistic goal in dementia. (While the older literature suggested that as many as 15 to 30% of dementias were “reversible,” more recent studies indicate that at most a few percent of dementias presenting to physicians are potentially reversible.)

Thus, the treating practitioner must begin by setting a realistic goal for therapeutic intervention. Symptom relief, alleviation of caregiver burden, prevention of complications (such as injury prevention or avoidance of aspiration pneumonia), and delay in progression of disease might be potential treatment targets. From this list, only symptom relief and delay in progression could be inferred from the studies examined in this systematic evidence review.

Outside the specialty clinic or clinical trial setting, most physicians have limited time and resources to expend on their patients with dementia. Few will have access to psychometrists or other individuals capable of administering extensive assessment instruments such as those used in clinical trials (e.g. ADAS-cog). Thus the typical practitioner must be able to complete a brief assessment, which provides sufficient information to determine whether a treatment is 1) indicated and 2) effective.

Deciding if a treatment is indicated depends upon the correct diagnosis (does this person have a dementia, and if so what type?), potential contraindications to the treatment (e.g. active peptic ulcer or heart block in the case of cholinesterase inhibitors), and the severity of disease. Determination of severity of dementia has given rise to several global scores such as the Global Deterioration Scale (GDS)[260] and the Clinical Dementia Rating (CDR)[261] In practice, the Mini-Mental State Examination (MMSE)[50] **(**a short, 30-item, cognitive screening test) is frequently used as a measure of severity. Not only is it part of the usual diagnostic protocol for suspected dementia, but it also has the advantage of being included in the entry criteria of many of the RCTs of anti-dementia medications. It is therefore useful for determining whether a patient fulfils the appropriate severity criterion for therapeutic intervention.

With regard to deciding whether a treatment is effective, much has been written about the relative importance of statistically significant and clinically significant changes in measures of cognition, function, and behavior in dementia. A distinction must be drawn between clinically detectable change and clinically meaningful change. While psychometric measures (standardized instruments, which are highly reliable and relatively free from the influence of judgment) may detect changes too small to be appreciated by the clinician, clinometric tools (measures that are based on a clinical judgment about an individual patient[262]) may be considered more relevant to practice. Results expressed as a change from baseline measured by clinometric instruments such as the Clinicians Interview Based Impression of Change (CIBIC) or its derivative the CIBIC plus, which incorporates observations of the caregiver, mimic clinical practice more closely than most psychometric tools. The CIBIC aims to cover multiple domains relevant to the clinician (i.e. cognitive, functional, and behavioral). Clinicians may therefore interpret statistically significant changes on the CIBIC or similar scales with more confidence than changes on the many psychometric scales used in therapeutic trials. However, if an effect size of ~0.5 or greater is included in the analysis of psychometric outcomes, one can be reasonably confident of a robust response to the treatment under investigation.

Another measure of efficacy is the response rate—the percentage of study participants who experience an improvement (defined as a change of a specific magnitude on one or more scales.) This figure is useful for the clinician who may then indicate to the individual with dementia the chances of a positive outcome from the planned treatment.

Clinicians are faced with a bewildering array of results from clinical trials. Convergence of results (different studies of the same medication showing similar results) or studies of drugs in the same class showing similar results may help to reassure clinicians that the results are genuine. Conversely, when trials show differing results, clinicians should be especially vigilant in accepting only the results of the more positive trials.

As always, the translation of clinical trial evidence into practice demands careful scrutiny by the practitioner. Attention to external validity (is my patient sufficiently similar to those in the clinical trial that I can expect the same result from treatment?), interpretation of the outcome measures (clinically as well as statistically significant benefit), and weighing potential risks against potential benefits remain the responsibility of the treating practitioner.

Limitations of the McMaster AHRQ Review

A systematic review that has evaluated 91 pharmacological interventions in 186 RCTs with high internal validity has several limitations. The studies selected for this review are English-language trials. Based on our search results, we estimate that we could have potentially retrieved 1385 foreign-language articles (after de-duplication 1213) distributed among databases as follows: 346 from Cochrane Central, 444 from EMBASE, 559 from MEDLINE/PreMedline® 36 from other databases before review for title and abstract. If we assumed the same rate of potentially eligible studies for these non-English studies, an additional 16 non-English studies may have been eligible for review. It is possible that agents, such as Ginkgo biloba, may have had important trials published in non-English languages. The budget and timelines available, however, were a limiting factor to obtaining, translating, and abstracting non-English trials.

Secondly, no contact with authors of the eligible trials was undertaken to collect additional unpublished studies or provide results/data that were not presented in the published article. Although contact with the original authors of the trials (to supplement the missing information from the included studies) could have compensated for many of the reporting challenges we encountered, this strategy was not feasible given the timeline of this systematic review. Our experience at the McMaster EPC suggests that the majority of authors do not respond in a timely fashion if at all. Additionally, efforts were not made to contact industry for unpublished trials. It is likely that industry sponsors of trials that are not published in the public domain are under no obligation to share trials (particularly negative trials). Not contacting authors of eligible trials for additional data and not attempting to locate unpublished trials (either by other authors/ experts or by industry) may introduce publication bias in this systematic review.

Thirdly, we employed two eligibility criteria that may account for some differences in acceptance of well-known studies. The first of these was a minimum threshold for quality score as determined by the modified Jadad scale. Despite the fact that this scale has excellent reliability and content validity, some may argue that the threshold score of 3 is arbitrary and may have unnecessarily eliminated studies of historical importance. It is our view that given the amount of literature available, all efforts should be aimed at selecting only the trials with the highest internal validity rather than selecting the largest number of eligible trials.

The second eligibility criteria concerned the exclusion of crossover trials. Although crossover trials are suitable for chronic diseases, they may be prone to period effects or period-by-treatment interactions. Period effects are systematic changes in the outcome that apply to all patients due to temporal changes in the disease or to the measurement instrument. Period-by-treatment interactions occur when the efficacy of the intervention varies by period. This is a significant concern for studies that attempt to show disease modification and are carried out over a longer period of time. Additionally, a carry-over effect may occur if the washout period is not adequate. In addition to the weaknesses of this design, some limitations arise when considering the potential for meta-analytic analyses. Traditionally, first period data from a crossover trial are abstracted and can be potentially combined with parallel trials for analyses of a pooled estimate; the reporting of the study results (positive or negative) would also be based on this first period data. In a preliminary phase of the review, several crossover trials were examined. It was noted that many did not report first period data, which precludes any potential for combining with parallel trials; many trials also did not undertake statistical tests during the first experience, thus making it difficult to report the direction of the findings, even if the trial could be combined. Finally, the TEP considered the fact that this systematic review was evaluating a variety of drug interventions administered over differing time intervals, and so period effects might be an important source of bias. For all these reasons, the TEP made the decision to exclude crossover trials from this systematic review. Thus, this review is limited to evidence based on high-quality parallel trials only.

A final limitation to our study was the use of a checklist developed to address the issue of quality of reporting adverse events. The Jadad scale was not designed to evaluate the quality of reporting adverse events. Thus, when determining the "harms" or risks associated with an intervention, the quality or "internal validity" of collecting and reporting these adverse events needed to be evaluated. Although our checklist has face validity, it has not undergone formal psychometric testing.

Future Research Recommendations

The findings of this report suggest several important areas for future research on pharmacological treatments for dementia. These include:

Analytic Framework of the intended aim of the therapy on the disease

- Better conceptualization and research design to capture "delay in progression".
- Clearer consensus on defining efficacy (benefits and clinically important change).
- Longer term studies (> 12 months).

Potential for bias

- Clarification of the role of industry sponsorship; one recommendation should be that all studies are required to disclose such information in future, including who analyzed the results.
- More concerted effort to incorporate unpublished studies and negative trials in future reviews.

Population

- Inclusion of the spectrum of severity in the patient populations (there is nothing to suggest that severe patients may not benefit from pharmacotherapy aimed at cognitive function improvement).
- The need for validation of trials and testing processes within cultures other than the traditional white population.
- Examining the efficacy of interventions in different sub-populations (age, disease severity levels, etc.).
- Better measurement and reporting of important patient characteristics (including baseline cognition scores, co-morbid conditions, the use of other medications, etc.).
- Inclusion of MCI type groups of subjects to evaluate “delay of onset”.

Outcomes

- Expansion of outcomes collected to include more than just cognitive function, and especially include caregiver burden and quality of life/ADL.
- Clear operational definitions for determining critical outcomes (delay to onset, delay to progression, important effect size, etc).
- Better understanding of how outcomes perform cross-culturally.
- Production of other diagnostic instruments to detect both onset and responses to therapies across varied cultural groups.
- Improvement in the reporting of adverse events to evaluate harm.

Analysis

- Appropriate analytical strategies that take into account intention to treat (ITT)/ last observation carried forward (LOCF) analyses; where possible both observed case and ITT/LOCF analyses should be presented.
- Sufficient data to estimate effect size, taking into account variability in both treated and control populations on the primary measures.
- Reporting the power of the study when findings are non-significant.

Intervention

- Undertake more studies with direct comparison of drugs to determine the relative efficacy of agents.
- Improved description of the titration process.
- Improved collection of adverse events undertaken in a systematic fashion with standardized instruments.

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Acronyms and Abbreviations

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AAMI	Age-Associated Memory Impairment
ABID	Agitated Behavior Inventory for Dementia
ABS	Adaptive Behavior Scale
ACES	Agitation-Calmness Evaluation Scale
ACFP	American College of Family Physicians
AChE	Acetycholinesterase
ACP-ASIM	American College of Physicians – American Society of Internal Medicine
ACPT	Auditory Continuous Performance Test
ACTH	Adrenocorticotropic homone
AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-11; ADAS-13	Alzheimer's Disease Assessment Scale (11 and 13 items)
ADAS-Cog ADAS-NonCog	Alzheimer's Disease Assessment Scale-Cognitive and Non-Cognitive Sections
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale
ADL; ADLC	Activities of Daily Living (Checklist)
ADL-BDRS	Activities of Daily Living-Blessed Dementia Rating Scale
ADL-PDS	Activities of Daily Living- Progressive Deterioration Scale
ADS	Alzheimer's Deficit Scale
ADSS	Alzheimer's Disease Symptomatology Scale
AFBS	Aversive Feeding Behavior Scale
AGGR	Aggressiveness subscale of the Personality Psychopathology Five (PSY-5) Scales
AGS-E	Assessment of Global Symptomatology-Elderly
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immune Deficiency Syndrome
AIMS	Abnormal Involuntary Movement Scale
ALCAR	Carnitine
AMED	Allied and Complementary Medicine Database
AMI	Attention Matrices
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid
AMTS	Abbreviated Mental Test Score
APOE	Apolipoprotein E gene
BADL	Basic Activities of Daily Living
BARS, BAS	Barnes Akathisia Rating Scale
BCRS	Brief Cognitive Rating Scale
BDI	Beck Depression Inventory
BDRS	Blessed Dementia Rating Scale
BEHAVE – AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BePU	Berlin rating scale for psychomotoric restlessness
Bf-S	Zerssen Adjective Mood Scale (German test: Befindlichkeitsskala)
BGP	Behavioural Rating Scale for Geriatric Patients
BGP	Behavioural Rating Scale for Geriatric Patients
BI	Barthel Index
bid	Twice a day
BL-A	Blessed A scale
Blessed-D BDRS	Blessed Dementia Rating Scale
BMI	Body Mass Index
BMICT	Blessed Memory Information and Concentration Test
BMY	Nootropic agent; Bristol-Myers Squibb
BNT	Boston Naming Test
BPRS	Brief Psychiatric Rating Scale

Acronyms and Abbreviations cont'd.

BRMS	Bech-Rafaelsen Mania Scale
BRSD	Behavioral Rating Scale for Dementia
BSRT	Babcock Story Recall Test
BSRT	Buschke Selective Reminding Test
BSS	Behavioral Syndromes Scale for Dementia
BTT	Block Tapping Test
CADISIL	Cerebral Autosomal Dominant Ischemia with Subcortical Leukoencephalopathy
CAMCOG	Cognitive section of the Cambridge Examination for Mental Disorders in the Elderly
CAMDEX	Cambridge Examination for Mental Disorders in the Elderly
CAMTOT	CAMCOG Total Score
CANTAB	Cambridge Automated Neuropsychological Test Assessment Battery
CAPE	Clifton Assessment Procedures for the Elderly
CASE	Clifton Assessment Scale for the Elderly
CASI	Cognitive Abilities Screening Instrument
CATS	Caregiver's Activity Time Survey
CAUST	Canadian Utilization of Service Tracking questionnaire
CBC	Complete Blood Count
CBM 36-733	2-methyl-alpha-ergokryptine
CCASSS	Computerized Cognitive Assessment System Speed Score
CCT	Controlled Clinical Trial
CDR, CDRS CDR-NH CDR-SB	Clinical Dementia Rating; Clinical Dementia Rating Scale Clinical Dementia Rating – Nursing Home Version Clinical Dementia Rating – Sum of Boxes
CDT	Clock-Drawing Test
CEB	Clinical Epidemiology and Biostatistics
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CERE	Cerebrolysin
CETM	Dynamic measure of comprehension process (Spilich)
CGAE	Clinical Global Assessment of Efficacy
CGC+	Clinical Global Change-Plus
CGI	Clinical Global Impression
cGIC	Caregiver-rated Global Impression of Change
CGIC	Clinical Global Impression of Change
CGI-GI	Global Improvement
CGI-CGC	Clinical Global Impression-Clinical Global Change
CGI-S; CGI-S/C	Clinical Global Impression-Severity/Change
CGRS	Clinicians' Global Rating Score
chisq	Chi-Square Test
$chisq_{M-H}$	Mantel-Haenszel Chi-Square Test
CI	Confidence interval
CIBI	Clinician's Interview-Based Impression
CIBIC	Clinician's Interview-Based Impression of Change
CIBIC+	Clinician's Interview Based Impression of Change plus Caregiver
CIBIS+	Clinician's Interview-Based Impression of Severity with Caregiver Input
CINAHL	Cumulative Index to Nursing & Allied Health Literature ®
CIND	Cognitive Impairment Not yet Diagnosed
CLEX	Clinical Examination
CloND	Cognitive Loss No Dementia
CMAI	Cohen Mansfield Agitation Inventory
CNTB	Computerized Neuropsychological Test Battery
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
COWAT	Controlled Oral Word Association Test
CPRS	Comprehensive Psychopathological Rating Scale
CPT	Cognitive Performance Test
CSDD	Cornell Scale for Depression in Dementia
CSGDS	Collateral Source Geriatric Depression Scale
CSI	Caregiver Stress Inventory

Acronyms and Abbreviations cont'd.

CSS	Caregiver Stress Scale
CT	Computerized Tomography
CVD	Cerebrovascular Disease
CVLT	California Verbal Learning Test
d	day
d	Effect Size Value – (d) is the average amount of change in standard deviation units achieved by individuals in a treated group versus the change achieved by members of a control/comparison group for a particular study
DAD	Disability Assessment for Dementia
DAT	Dementia Alzheimer's Type
D-B	Delay relative to Baseline
DBDS	Dementia Behavior Disturbance Scale
DCT	Digit Copying Test
DDAVP	Deamino-D-Arginine-Vasopressin
DEK	Dihydroergokryptine
Df	Degrees of Freedom
DMR	Dementia Questionnaire for Mentally Retarded Persons
DMSE	Delayed Matching-to-Sample Exam
D-P	Delay relative to Placebo
DPZ	Donepezil
DRS	Dementia Rating Scale
DSCS	Depressive Symptoms Collateral Source
DSM	Diagnostic and Statistical Manual of Mental Disorders (Edition III, III-R, IV)
DSPT	Digit Span Test
DSS	Depressive Signs Scale
DST; DSST	Digit Symbol (Substitution) Test
DTIC	Discovering Things in Common
e.g.,	example
ECG	Electrocardiogram
EEG	Electroencephalography
EFR	Emotional Face Recognition
EIS	Efficacy Index Score
EMBASE	Excerpta Medica Database
EPS	Extrapyramidal Symptoms
ERP	Event-Related Potential
ESRS	Extrapyramidal Symptom Rating Scale
FAST	Functional Assessment Staging
FCCA	Final Comprehensive Consensus Assessment
FCMT	Figure Copy/ Memory Test
FDA	Food and Drug Administration
FDG-PET	Positron Emission Tomography with 18-fluorodeoxyglucoseis
FIGT	Figure Detection Test
FIM	Functional Independence Measure
FRS	Functional Rating Scale test
g	gram
GABA	Gamma-aminobutyric acid
GBS	Gottfries-Bråne-Steen
GBS-SDS	Gottfries-Bråne-Steen – Scale for Dementia Syndromes
GDS	Global Deterioration Scale
GERRI	Geriatric Evaluation by Relative's Rating Instrument
GIS	Global Improvement Scale
GM-1	Monosialoganglioside
GMS-A	Geriatric Mental State questionnaire
GPI-E	General Psychiatric Impression-Elderly
GS	Gestalt Scale
h	hour
HAM-A; HARS	Hamilton Anxiety Rating Scale

Acronyms and Abbreviations cont'd.

HAM-D; HDRS	Hamilton Depression Rating Scale
HDS-R	Hasegawa Dementia Scale-Revised
HIS	Hachinski Ischemic Score
HIV	Human Immunodeficiency Virus
HMII	Hachinski-Marshall Ischaemic Index
HVLT	Hopkins Verbal Learning Test
IADL	Instrumental Activities of Daily Living
ICC	Item Characteristic Curve analysis
ICD	International Classification of Diseases (Version 9 or 10)
IDDD	Interview for Deterioration in Daily Living Activities in Dementia-complex task
IF	Industry Funded
IM	Intramuscular
I-P	Improvement relative to Placebo
IPSC-E	Raskin's and Crook's Inventory of Psychic and Somatic Complaints for the Elderly
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IS	Industry provided Supplies
ITT	Intention-to-treat
IU	International Units
kg	kilogram
KOLT	Kendrick Object Learning Test
LAS	Luria Alternating Series
lbs	pounds
LFT	Liver Function Test
LMT	Logical Memory Test
LNNB	Luria-Nebraska Neuropsychological Battery
LOCF	Last Observation Carried Forward
LPRS	London Psychogeriatric Rating Scale
LRU	Lipasemic Releasing Units
m	month
M	male
MAACL-R	Multiple Affect Adjective Checklist-Revised
MACF	Microtubule Actin Crosslinking Factor
MADR-S	Montgomery-Asberg Depression Rating Scale
MCI	Mild Cognitive Impairment
MCPT	Modified Continuous Performance Test
MDB	Mental Deterioration Battery
MeSH	Medical Subject Heading
µg	microgram
mg	milligram
MID	Multi Infarct Dementia
Min	Minimal
MITT	Modified Intention-to-treat
ml	milliliter
MMSE (MMSE-CE) CMMSE MMMSE SMMSE	Mini-Mental Status Exam (estimated score) Cantonese MMSE Modified MMSE Standardized MMSE
MNLT	Modified Names Learning Test
Mod	Moderate
Modly Sev	Moderately Severe
MQ	Memory Quotient
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MU-EPC	McMaster University Evidence-based Practice Center
MWF	Mattis Word Fluency
MX	Mixed results
n	number included in study
N	No

Acronyms and Abbreviations cont'd.

NA	Not available
NAA	Nuremberg gerontopsychological inventory for Assessing Activities of daily living
NAB	Nurnberger-Alters-Beobachtungs-Skala
NAC	N-Acetylcysteine
NAI	Nuremberg Age Inventory
NART	Nelson Adult Reading Test
NCT	Number Connection Test
NDT	New Dot Test
NI	Non-Industry funding source
NIMCS	Newcastle Memory, Information and Concentration Scale
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NLT	Names Learning Test
NMDA	N-methyl-D-aspartate
NMICS	Newcastle Memory, Information and Concentration Scale
NMS	Nowlis Mood Scale
NNI	Number Needed to Intervene
NOSGER	Nurses Observation Scale for Geriatric Patients
NOSGER-IADL	Nurses Observation Scale for Geriatric Patients – Instrumental Activities of Daily Living subscale
NOSIE	Nurses Observation Scale for Inpatients
NPI (NPI-4, NPI-10)	Neuropsychiatric Inventory Subscores 4,10
NPI-NH	Neuropsychiatric Inventory – Nursing Home Version
NR	Not Reported
NRSMG	Non-Randomised Studies Methods Group
NS	Not significant
NSL	Neuropsychological Aging Self-Evaluation – List for Age Symptoms
NST	Non-Stress Test
NT	Not tested
OARS – ADL	Older Americans Resource Scale
OAS	Overt Aggression Scale
OC	Observed Cases
OLT	Object Learning Test
OMDR	Oculomotor Delayed Response
OR	Odds Ratio
ORG 2766	Adrenocorticotropic hormone derivative
OXIR	Oxiracetam
oz	ounce
p	p value
P300	Electrophysiological potential that is indicator of associative and cognitive processes and latency in decision making processes
PAD	Presenile Alzheimer's Disease
PADL	Performance of Activities of Daily Living
PANSS-EC	Positive and Negative Syndrome Scale-Excited Component
PD	Parkinson's Disease
PDD	Progressive Degenerative Dementia
PDS	Progressive Deterioration Scale
PDSD	Primary Degenerative Senile Dementia
PET	Positron Emission Tomography
PGIR	Patient's Global Improvement Rating
PI	Partially funded by Industry
PICD	Presenile Idiopathic Cognitive Decline
POMS	Profile of Mood States
PRL	Prolactin

Acronyms and Abbreviations cont'd.

PSMS	Physical Self-Maintenance Scale
PSP	Progressive Supranuclear Palsy
PSQI	Pittsburgh Sleep Quality Index
qid	Four times daily
QoL	Quality of Life
R	Correlation Coefficient
RA	Research Assistant
RAGS; RAGS-E	Relative's Assessment of Global Symptomatology (Elderly)
RAPSU	Scale for psychomotoric agitation
R-AVL	Rey auditory-verbal-learning test
RCT	Randomized Controlled Trial
RDS	Rapid Disability Scale
RefMan	Reference Manager Version 10®
RGRS	Relatives' Global Rating Score
RMBPC	Revised Memory and Behavior Problems Checklist
RMT RMT-A&R RMT-DR RMT-MI	Rey Memory Test; Randt Memory Test Randt Memory Test – Acquisition and Recall Randt Memory Test – Delayed Recall Randt Memory Test – Memory Index
RPM	Raven's Progressive Matrices
RPT	Rivermead Behavioural Memory Test-Profile Score
RR	Relative Risk
RT	Reaction Time
RTI	Research Triangle Institute
SADS	Schedule for Affective Disorders and Schizophrenia
SAS	Simpson-Angus Scale
SAS-G	Self Assessment Scale – Geriatric
S-B	Stabilization relative to Baseline
SBI	Spontaneous Behavior Interview
SC	Significant change
SCAG	Sandoz Clinical Assessment – Geriatric
SCB	Screen for Caregiver Burden
SCWIT	Stroop Color Word Interference Test
SD	Standard Deviation
SDAT	Senile Dementia of the Alzheimer's Type
SEM	Standard Error
Sev	Severe
SF-36	Medical Outcomes Study Short-Form 36-Item Health Survey
SGRS	Stockton Geriatric Rating Scale
SHGRS	Stuard Hospital Geriatric Rating Scale
SIB	Severe Impairment Battery
SIP	Sickness Impact Profile
SKT	Syndrome Kurz test; Syndrome Short Test
SMQ	Squire's Memory Questionnaire
SMST	Sternberg's Memory Scanning Test
SPECT-TcHMPAO	Single Photon Emission Computed Tomography with hexamethylpropyleneamineoxime
SPET	Single Photon Emission Tomography
SRT SRT-DR	Selective Reminding Procedure Selective Reminding Procedure-Delayed Recall
SWFT	Semantic Word Fluency Test
TEP	Technical Expert Panel
TESS	Treatment Emergent Symptom Scale
TESS-DOTES	Dosage Record and Treatment Emergent Symptom Scales
tid	Three times daily
TK	Token Test
TOO	Task Order Officer
TP	Toulouse Piéron
TPAT	Toulouse-Pieron Attention Test

Acronyms and Abbreviations cont'd.

TSI	Test for Severe Impairment
UK	United Kingdom
UKU	Side effect rating scale
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VaD	Vascular Dementia
VAMS	Visual Analog Mood Scale
VAS	Visual Analogue Scales
VHB	Videorecorder Home-Behavioral assessment
vs.	versus
w	week
WAIS	Wechsler Adult Intelligence Scale
WAIS-DI	Deterioration Index
WAIS-DSPT	Wechsler Adult Intelligence Scale – Digit Span Test
WAIS-DSST	Wechsler Adult Intelligence Scale –Digit Symbol Substitution Test
WAIS-DTIC	Wechsler Adult Intelligence Scale – Discovering Things in Common
WAIS-VOC	Wechsler Adult Intelligence Scale-Vocabulary Subset
WHO	World Health Organization
WLM	Word List Memory test
WMS-MQ	Wechsler Memory Scale-Memory Learning Restoration
WMS-R	Wechsler Memory Scale-Revised
x^2	chi-square
y	year
Y	yes
ZVT	Zahlen-Verbindungs Test -Trail Making Test

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Status: *Not included because dementia population not randomized to treatment*

Wooltorton E. Risperidone (Risperdal): Increased rate of cerebrovascular events in dementia trials. CMAJ 2002 Nov 26; 167(11):1269-70.
Status: *Not included because not a full article*

World Health Organization. The tenth revision of the International Classification of Diseases and relative health problems (ICD-10). Geneva: WHO; 1992.
Status: *Background article*

Wouters-Wesseling W, Wouters AE, Kleijer CN, et al. Study of the effect of a liquid nutrition supplement on the nutritional status of psycho-geriatric nursing home patients. Eur J Clin Nutr 2002 Mar; 56(3):245-51.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wright LK, Litaker M, Laraia MT, et al. Continuum of care for Alzheimer's disease: A nurse education and counseling program. Issues Ment Health Nurs 2001 Apr; 22(3):231-52.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Wroblewski T, Silvestre J, Castaner J. JTP-4819. Cognition enhancer, prolyl endopeptidase inhibitor. Drugs of the Future 1998; 23(4):384-9.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wu SF, Xie SZ, Lu WJ, et al. Comparison of the clinical effects of capsules and tablets in a randomized double-blind treatment of mild and moderate Alzheimer's disease. Shanghai Medical & Pharmaceutical Journal 1999; (8):36-8.
Status: *Article not retrievable*

Xiao S, Yan H, Yao P, et al. The efficacy of cerebrolysin in patients with vascular dementia: Results of a Chinese multicentre, randomised, double-blind, placebo-controlled trial. Hong Kong Journal of Psychiatry 1999; (2):13-9.
Status: *Included*

Xiao S, Yan H, Yao P, et al. Efficacy of FPF 1070 (cerebrolysin) in patients with Alzheimer's disease: A multicentre, randomised, double-blind, placebo-controlled trial. Clin Drug Investig 2000; (1):43-53.
Status: *Included*

Xiao SF, Yan HE, Yao BF, et al. A multi-center, double blind, placebo-controlled trial of the efficacy of cerebrolysin in treatment of vascular dementia. J Clin Psychol Med 1999; (1):1-3.
Status: *Article not retrievable*

XiaoSF, Yan HQ, Yao PF, et al. The efficacy of cerebrolysin in patients with Alzheimer disease. Mod Rehab 2000; (11):1624-5.
Status: *Article not retrievable*

Xu H, Shao N, Cui D, et al. A clinical study of yi zhi capsules in prevention of vascular dementia. J Tradit Chin Med 2000 Mar; 20(1):10-3.
Status: *Not included because Jadad Quality Scale score less than three*

Xu SS, Gao ZX, Weng Z, et al. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li Xue Bao/Acta Pharmacologica Sinica 1995 Sep; 16(5):391-5.
Status: *Included*

Xu SS, Cai ZY, Qu ZW, et al. Huperzine-A in capsules and tablets for treating patients with Alzheimer disease. Zhongguo Yao Li Xue Bao/Acta Pharmacologica Sinica 1999; 20(6):486-90.
Status: *Included*

Xu SS, Zhi X, Weng Z, et al. Efficacy of tablet huperzine-A on memory, cognition and behavior in Alzheimer's disease. Int Med J 1997; (2):127-31.
Status: *Duplicate publication*

Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. N Engl J Med 2001 Apr 19; 344(16):1207-13.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yamamoto Y, Akiguchi I, Oiwa K, et al. Twenty-four-hour blood pressure changes in the course of lacunar disease. Cardiovasc Dis 2001; 11(2):100-6.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yehuda S, Rabinovtz S, Carasso RL, et al. Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life. Int J Neurosci 1996 Nov; 87(3-4):141-4.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yesavage JA, Hollister LE, Burian E. Dihydroergotoxine: 6-mg versus 3-mg dosage in the treatment of senile dementia. Preliminary report. J Am Geriatr Soc 1979 Feb; 27(2):80-2.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yesavage JA, Westphal J, Rush L. Senile dementia: Combined pharmacologic and psychologic treatment. J Am Geriatr Soc 1981; 29(4):164-71.
Status: *Not included because dementia population not randomized to treatment*

Yesavage JA, Tinklenberg JR, Hollister LE, et al. Effect of nafronyl on lactate and pyruvate in the cerebrospinal fluid of patients with senile dementia. J Am Geriatr Soc 1982; 30(2):105-8.
Status: *Not included because dementia population not randomized to treatment*

Zanetti O, Frisoni GB, De Leo D, et al. Reality orientation therapy in Alzheimer disease: Useful or not? A controlled study. Alzheimer Dis Assoc Disord 1995; 9(3):132-8.
Status: *Not included because dementia population not randomized to treatment*

Zanetti O, Bianchetti A, Trabucchi M. Cost effectiveness of non pharmacological interventions in Alzheimer's disease. J Am Geriatr Soc 1998 Nov; 46(11):1481
Status: *Not included because not a full article*

Zanetti O, Zanieri G, Di Giovanni G, et al. Effectiveness of procedural memory stimulation in mild Alzheimer's disease patients: A controlled study. Neuropsychol Rehab 2001; (3-4):263-4.
Status: *Not included because dementia population not randomized to treatment*

Zank S, Schacke C. Evaluation of geriatric day care units: effects on patients and caregivers. J Gerontol B Psychol Sci Soc Sci 2002 Jul; 57(4):348-57.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zappoli R, Arnetoli G, Paganini M, et al. Contingent negative variation and reaction time in patients with presenile idiopathic cognitive decline and presenile Alzheimer-type dementia. Preliminary report on long-term nicergoline treatment. Neuropsychobiology 1987; 18(3):149-54.
Status: *Not included because Jadad Quality Scale score less than three*

Zappoli R, Arnetoli G, Paganini M, et al. Topographic bit-mapped event-related neurocognitive potentials and clinical status in patients with primary presenile mental decline chronically treated with nicergoline. Curr Ther Res Clin Exp 1991; 49(6):1078-97.
Status: *Not included because Jadad Quality Scale score less than three*

Zarit SH, Zarit JM, Reever KE. Memory training for severe memory loss: Effects on senile dementia patients and their families. Gerontologist 1982; 22(4):373-7.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zec RF, Trivedi MA. The effects of estrogen replacement therapy on neuropsychological functioning in postmenopausal women with and without dementia: A critical and theoretical review. Neuropsychol Rev 2002; 12(2):65-109.
Status: *Background article*

Zemlan FP, Folks DG, Goldstein BJ, et al. Velnacrine for the treatment of Alzheimer's disease: A double-blind, placebo-controlled trial. J Neural Transm Gen Sect 1996; 103(8-9):1105-16.
Status: *Included*

Zemlan FP, Keys M, Richter RW, et al. Double-blind placebo-controlled study of velnacrine in

Alzheimer's disease. Life Sci 1996; 58(21):1823-32.
Status: *Not included because Jadad Quality Scale score less than three*

Zhang LX, Wang TH, Zhong XS. Comparison of effects between malloryl and chlorpromazine on type I dementia praecox. J Guandong Med Coll 1999; (2):122-3.
Status: *Article not retrievable*

Zhou XH, Higgs RE. Assessing the relative accuracies of two screening tests in the presence of verification bias. Stat Med 2000 Jun 15; 19(11-12):1697-705.
Status: *Background article*

Ziemba C, Foster G, Neufeld R, et al. Haloperidol holiday: Is it a beneficial vacation for some nursing home residents? Clin Gerontol 1997; 17(3):15-24.
Status: *Not included because no extractable data relevant to review*

Zissis NP, Alevizos V, Dontas AS. Flunarizine, an inhibitor of Casup +sup 2-induced vascular constriction in geriatric patients. Curr Ther Res Clin Exp 1991; 29(3I):395-400.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. Neurology 2001 Oct 9; 57(7):1239-47.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Zwerling I, Plutchik R, Hotz M, et al. Effects of a procaine preparation (Gerovital H3) in hospitalized geriatric patients: A double-blind study. J Am Geriatr Soc 1975 Aug; 23(8):355-9.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Zill P, Burger K, Behrens S, et al. Polymorphisms in the alpha-2 macroglobulin gene in psychogeriatric patients. Neurosci Lett 2000 Nov 17; 294(2):69-72.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zimmer JG, Eggert GM, Chiverton P. Individual versus team case management in optimizing community care for chronically ill patients with dementia. J Aging Health 1990; 2(3):357-72.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zisselman MH, Rovner BW, Shmuely Y, et al. A pet therapy intervention with geriatric psychiatry inpatients. Am J Occup Ther 1996 Jan; 50(1):47-51.

Pharmacological Treatment of Dementia

Appendixes

Appendix A: Search Strings
Appendix B: Sample Data Extraction Forms
Appendix C: Evidence Tables
Appendix D: Peer Reviewers
Appendix E: Outcome measures
Appendix F: List of excluded studies

Prepared for:
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Appendix A

Search strategies

Appendix A.

Database: Cochrane Central Register of Controlled Trials <4th Quarter 2002> on OVID

Search strategy executed on February 3, 2003
Same search executed on February 4th, 2003 on the online version of the Cochrane Library for the new references <1st Quarter 2003>:

1 (mild cognitive impairment or MCI).tw.
2 ((cognitive impairment not dementia) or CIND).tw.
3 ((cognitive loss not dementia) or CLOND).tw.
4 Delirium, Dementia, Amnestic, Cognitive Disorders/
5 exp Amnesia/
6 Cognition Disorders/
7 exp Dementia/
8 exp tauopathies/
9 dement:.tw.
10 Alzheimer:.tw.
11 Huntington disease/
12 Lewy: ajd8 bod:.tw.
13 ((cognit: or memory or mental:) adj8 (decli: or impair: or los: or deteriorat:)).tw.
14 (chronic adj8 cerebrovascular).tw.
15 supra-nuclear palsy.tw.
16 (normal pressure hydrocephalus adj8 shunt:).tw.
17 benign senescent forgetfulness.tw.
18 (cerebr: adj8 deteriorat:).tw.
19 cerebr: ajd8 insufficien:.tw.
20 (confusion: or confused).tw.
21 (pick: adj8 disease).tw.
22 (creutzfeldt: or JCD: or CJD:).tw.
23 (Huntington: or Huntingdon).tw.
24 Binswanger:.tw.
25 brain atrophy.tw.
26 exp Cerebral Amyloid Angiopathy/
27 neurofibrillary tangles/
28 senile plaques/
29 neuropil threads/
30 spongiform encephalopathy.tw.
31 exp Hypothyroidism/
32 neurosyphilis/
33 exp amyloid beta-protein/ not (Down syndrome/ or trisomy 21.tw.)

34 (CADISIL or cerebral autosomal dominant ischemia with subcortical leukoencephalopathy).tw.
35 (corticobasil ganglionic degeneration or cortical basal degeneration or corticabasal ganglionic degeneration).tw.
36 multisystem atrophy.tw.
37 exp alcohol amnestic disorder/
38 (alcohol adj3 amnestic).tw.
39 or/1-38

Database: Pre-MEDLINE, MEDLINE on OVID
Search strategy executed on February 4, 2003

---

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 controlled clinical trials/
4 (clinical trials, phase II or clinical trials, phase III or clinical trials, phase IV or multicenter studies).sh.
5 random allocation.sh.
6 double blind method.sh.
7 cross-over studies.sh.
8 single-blind method.sh.
9 clinical trial.pt.
10 (clin: adj25 trial:).ti,ab.
11 ((singl: or doubl: or trebl: or tripl:) adj25 (blind: or mask:)).ti,ab.
12 placebos.sh.
13 placebo:.ti,ab.
14 random:.ti,ab.
15 or/1-14
16 comparative study.sh.
17 exp evaluation studies/
18 follow up studies.sh.
19 prospective studies.sh.
20 or/16-19
21 (tu or th).xs.
22 treatment outcome/
23 exp therapeutics/
24 or/21-23
25 20 and 24
26 15 or 25
27 (mild cognitive impairment or MCI).tw.
28 ((cognitive impairment not dementia) or CIND).tw.
29 ((cognitive loss not dementia) or CLOND).tw.
30 exp dementia/
31 exp tauopathies/
32 (dement: or alzheimer:).tw.
33 amentia.tw.
34 frontotemporal lobar degeneration.tw.
35 hiv-associated cognitive motor complex.tw.
36 encephalopathy, aids.tw.
37 encephalopathy, hiv.tw.
38 mesulam syndrome.tw.
39 progressive nonfluent aphasia.tw.
40 binswanger disease.tw.
41 binswanger encephalopathy.tw.
42 leukoencephalopathy, subcortical.tw.

43 subcortical arteriosclerotic encephalopathy.tw.
44 chronic progressive subcortical encephalopathy.tw. or alcohol amnestic disorder/ or alcohol induced disorders, nervous system/ or (alcohol adj3 amnestic).tw. or (alcohol adj2 dysmestic).tw. or (ethanol adj3 nervous system disorders).tw. or ethyl alcohol abuse neurologic syndromes.tw.
45 (lewy: bod: adj8 disease).tw.
46 brain atrophy, circumscribed lobar.tw.
47 (pick: adj8 disease).tw.
48 exp amyloid beta-protein/ not (down syndrome/ or trisomy 21.tw.)
49 exp cerebral amyloid angiopathy/
50 neurofilament proteins/
51 tau proteins/
52 neurofibrillary tangles/
53 neuropil threads/
54 senile plaques/
55 (Corticobasil ganglionic degeneration or cortical basal degeneration or cortica).tw.
56 (CADISIL or Cerebral autosomal dominant ischemia with subcortical leukoencephalopathy).tw.
57 Multisystems atrophy.tw.
58 huntington disease/
59 hydrocephalus, normal pressure/
60 Creutzfeldt-Jakob syndrome/
61 spongiform encephalopathy.tw.
62 (cjd or jcd).tw.
63 Creutzfeldt-Jakob disease.tw.
64 spongiform encephalopathy.tw.
65 exp Hypothyroidism/
66 exp Vitamin B 12 Deficiency/
67 exp Neurosyphilis/
68 or/27-67
69 26 and 68
70 animal.sh.
71 69 not 70
72 71 not (comment or editorial or news or letter).pt.
73 72 and eng.la.
74 limit 73 to yr=1998-2003

Database: EMBASE <1996 to 2003 Week 5> on OVID
Search strategy executed on February 6, 2003
---

1 (mild cognitive impairment or MCI).tw.
2 ((cognitive impairment not dementia) or CIND).tw.
3 ((cognitive loss not dementia) or CLOND).tw.
4 exp dementia/
5 (dement: or alzheimer:).tw.
6 amentia.tw.
7 frontotemporal lobar degeneration.tw.
8 hiv-associated cognitive motor complex.tw.
9 encephalopathy, aids.tw.
10 encephalopathy, hiv.tw.
11 mesulam syndrome.tw.
12 progressive nonfulent aphasia.tw.
13 binswanger disease.tw.
14 binswanger encephalopathy.tw.
15 leukoencephalopathy, subcortical.tw.
16 subcortical arteriosclerotic encephalopathy.tw.
17 chronic progressive subcortical encephalopathy.tw.
18 exp Korsakoff psychosis/ or exp Wernicke Korsakoff syndrome/
19 (alcohol adj3 amnestic).tw.
20 (alcohol adj2 dysmnestic).tw.
21 (ethanol adj3 nervous system disorders).tw.
22 ethyl alcohol abuse neurologic syndromes.tw.
23 (Lewy: bod: adj8 disease).tw.
24 brain atrophy, circumscribed lobar.tw.
25 (Pick: adj8 disease).tw.
26 exp brain atrophy/ or exp brain cortex atrophy/ or exp brain degeneration/ or exp corticobasal degeneration/ or exp lewy body/ or exp neurofibrillary tangle/ or exp neuropil thread/ or exp organic brain syndrome/
27 exp amyloid beta-protein/ not (exp Down syndrome/ or trisomy 21.tw.)
28 exp Vascular Amyloidosis/
29 exp Neurofilament Protein/
30 Tau Protein/
31 Neurofibrillary Tangle/
32 Neuropil Thread/
33 Senile Plaque/
34 (corticobasil ganglionic degeneration or cortical basal degeneration or corticobasal degeneration).tw.
35 (CADISIL or Cerebral autosomal dominant ischemia with subcortical leukoencephalopathy).tw.
36 multisystems atrophy.tw.
37 Normotensive Hydrocephalus/
38 Creutzfeldt Jakob Disease/
39 exp Brain Spongiosis/

40 spongiform encephalopathy.tw.
41 (CJD or JCD).tw.
42 Creutzfeldt-Jakob disease.tw.
43 exp Hypothyroidism/
44 Cyanocobalamin Deficiency/
45 Neurosyphilis/
46 or/1-45
47 multicenter study/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or randomized controlled trial/ or exp postmarketing surveillance/
48 randomization/
49 crossover procedure/ or double blind procedure/ or experimental design/ or latin square design/ or parallel design/ or single blind procedure/
50 (clin: adj25 trial:).ti,ab.
51 ((singl: or doubl: or trebl: or tripl:) adj25 (blin: or mask:)).ti,ab.
52 Placebo/
53 placebo:.ti,ab.
54 random:.ti,ab.
55 exp comparative study/ or exp drug comparison/
56 exp "evaluation and follow up"/
57 longitudinal study/ or major clinical study/ or prospective study/
58 or/47-54
59 or/55-57
60 (tu or th).fs.
61 exp treatment outcome/
62 exp therapy/
63 or/60-62
64 59 and 63
65 58 or 64
66 65 and 46
67 exp animal/
68 66 not 67
69 68 not (comment or editorial or news or letter or conference paper).pt.
70 limit 69 to English language
71 limit 70 to yr=1998-2003

Database: AMED (Allied and Complementary Medicine) <1985 to February 2003> on OVID
Search strategy executed on March 4, 2003
---

1 exp clinical trials/ or double blind method/ or random allocation/
2 clinical trial.pt.
3 (clin: adj25 trial:).ti,ab.
4 ((singl: or doubl: or trebl: or tripl:) adj25 (blind or mask:)).ti,ab.
5 placebos.sh.
6 placebo:.ti,ab.
7 random:.ti,ab.
8 or/1-7
9 (mild cognitive impairment or MCI).tw.
10 ((cognitive impairment not dementia) or CIND).tw.
11 ((cognitive loss not dementia) or CLOND).tw.
12 exp dementia/
13 (dement: or Alzheimer:).tw.
14 amentia.tw.
15 frontotemporal lobar degeneration.tw.
16 hiv-associated cognitive motor complex.tw.
17 (encephalopathy, aids or encephalopathy, hiv).tw.
18 mesulam syndrome.tw.
19 progressive nonfluent aphasia.tw.
20 binswanger disease.tw.
21 binswanger encephalopathy.tw.
22 leukoencephalopathy, subcortical.tw.
23 subcortical arteriosclerotic encephalopathy.tw.
24 chronic progressive subcortical encephalopathy.tw.
25 (alcohol adj3 amnestic).tw.
26 (alcohol adj2 dysmnestic).tw.
27 (ethanol adj3 nervous system disorders).tw.
28 ethyl alcohol abuse neurologic syndromes.tw.
29 (Lewy: bod: adj8 disease).tw.
30 brain atrophy, circumscribed lobar.tw.
31 (Pick: adj8 disease).tw.
32 (corticobasil ganglionic degeneration or cortical basal degeneration or cortica).tw.
33 (CADISIL or cerebral autosomal dominant ischemia with subcortical leukoencephalopathy).tw.
34 Multisystems atrophy.tw.
35 spongiform encephalopathy.tw.
36 (cjd or Jcd).tw.
37 Creutzfeldt-Jakob disease.tw.
38 hypothyroidism/
39 or/9-38
40 8 and 39
41 40 not (comment or editorial or news or letter).pt.

42 41 and English.lg.

Database: CINAHL <1982 to February Week 3 2003> on OVID
Search strategy executed on March 5, 2003
---

1 crossover design/ or empirical research/ or experimental studies/ or exp clinical trials/ or community trials/ or factorial design/ or quantitative studies/
2 clinical trial.pt.
3 (clin: adj25 trial:).ti,ab.
4 ((singl: or doubl: or trebl: or tripl:) adj25 (blind: or mask:)).ti,ab.
5 Placebos/
6 placebo:.ti,ab.
7 random:.ti,ab.
8 Study Design/
9 or/1-8
10 (mild cognitive impairment or MCI).tw.
11 ((cognitive impairment not dementia) or CIND).tw.
12 ((cognitive loss not dementia) or CLOND).tw.
13 exp Dementia/
14 (dement: or Alzheimer:).tw.
15 amentia.tw.
16 frontotemporal lobar degeneration.tw.
17 hiv-associated cognitive motor complex.tw.
18 (encephalopathy, aids or encephalopathy, hiv).tw.
19 mesulam syndrome.tw.
20 progressive nonfulent aphasia.tw.
21 Binswanger disease.tw.
22 Binswanger encephalopathy.tw.
23 leukoencephalopathy, subcortical.tw.
24 (chronic progressive subcortical encephalopathy or (alcohol adj3 amnestic) or (alcohol adj2 dysmestic) or (ethanol adj3 nervous system disorders) or ethyl alcohol abuse neurologic syndromes).tw.
25 Lewy body disease.tw.
26 brain atrophy, circumscribed lobar.tw.
27 Pick: disease.tw.
28 (corticobasil ganglionic degeneration or cortical basal degeneration or cortica).tw.
29 (CADASIL or cerebral autosomal dominant ischemia with subcortical leukoencephalopathy).tw.
30 multisystems atrophy.tw.
31 Huntington's Disease/
32 Creutzfeldt-Jakob Syndrome/
33 spongiform encephalopathy.tw.
34 (cjd or jcd).tw.
35 Creutzfeldt-Jakob disease.tw.
36 spongiform encephalopathy.tw.
37 exp Hypothyroidism/
38 Neurosyphilis/
39 or/10-38

40 9 and 39
41 40 not (editorial or letter or proceedings).pt.
42 limit 41 to English

Database: Ageline <1978 to December 2002> on SILVERPLATTER
Search strategy executed on March 6, 2003

#1 randomized controlled trials in DE
#2 controlled clinical trials in de
#3 random allocation
#4 controlled clinical trial*
#5 randomized controlled trial*
#6 random allocation
#7 double blind method
#8 single blind method
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 clinical trial*
#11 (clin* near trial*) in TI
#12 (clin* near trial*) in AB
#13 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
#14 (#13 in TI) or (#13 in AB)
#15 placebo*
#16 Placebo* in TI
#17 placebo* in AB
#18 random* in TI
#19 random* in AB
#20 research design
#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#22 mild cognitive impairment
#23 (cognitive impairment and dementia) or CIND
#24 (cognitive loss not dementia) or CLOND
#25 (explode 'Dementia-' in DE) or (explode 'Early-Onset-Dementia' in DE) or (explode 'Vascular-Dementia' in DE)
#26 dement* or alzheimer*
#27 amentia*
#28 frontotemporal lobar degeneration
#29 hiv-associated cognitive motor complex
#30 aids associated encephalopathy
#31 hiv associated encephalopathy
#32 mesulam syndrome
#33 progressive nonfluent aphasia
#34 binswanger disease
#35 binswanger encephalopathy
#36 leukoencephalopathy subcortical
#37 subcortical arteriosclerotic encephalopathy
#38 chronic progressive subcortical encephalopthy
#39 alcohol near amnestic
#40 alcohol amnestic disorder
#41 alcohol induced disorders

#42 alcohol near dysmnestic
#43 ethanol near nervous system disorders
#44 lewy* bod* near disease
#45 ethyl alcohol abuse neurologic syndromes
#46 brain atrophy lobar
#47 Pick* near disease*
#48 cerebral amyloid angiopathy
#49 neurofilament protein*
#50 tau protein*
#51 neurofibrillary tangles
#52 neuropil threads
#53 senile plaque*
#54 corticobasil ganglionic degeneration or cortical basal degeneration or cortica
#55 cadisil
#56 cerebral autosomal dominant ischemia with subcortical leukoencephalopathy
#57 multisystems atrophy
#58 explode 'Huntingtons-Disease' in DE
#59 normal pressure hydrocephalus
#60 Creutzfeldt-Jakob syndrome
#61 spongiform encephalopathy
#62 cjd or jcd
#63 Creutzfeldt-Jakob disease
#64 hypothyroidism
#65 vitamin b12 deficiency
#66 neurosyphilis
#67 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66
#68 #67 and #21
* #69 #68 and (DT=JOURNAL-ARTICLE)

Database: PsychINFO <1967 TO 2002/12> on SILVERPLATTER
Search strategy executed on March 7, 2003

#1 randomized controlled trial in PT
#2 controlled clinical trial in PT
#3 controlled clinical trials
#4 random allocation
#5 (clinical trial*) in DE,SU
#6 (random allocation) in DE,SU
#7 (double blind method) in DE,SU
#8 (cross-over studies) in DE,SU
#9 (single-blind method) in DE,SU
#10 (clinical trial) in PT
#11 ((clin* near trial*)) in TI
#12 (placebo*) in DE,SU
#13 (placebo*) in TI
#14 (random*) in TI
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 mild cognitive impairment
#17 MCI
#18 (cognitive impairment not dementia) or CIND
#19 (cognitive loss not dementia) or CLOND
#20 (explode 'AIDS-Dementia-Complex' in DE) or (explode 'Alzheimers-Disease' in DE) or (explode 'Dementia-with-Lewy-Bodies' in DE) or (explode 'Dementia-' in DE) or (explode 'General-Paresis' in DE) or (explode 'Multi-Infarct-Dementia' in DE) or (explode 'Presenile-Dementia' in DE) or (explode 'Senile-Dementia' in DE) or (explode 'Vascular-Dementia' in DE)
#21 dement* or Alzheimer*
#22 amentia
#23 HIV-associated cognitive motor complex
#24 encephalopathy aids
#25 encephalopathy hiv
#26 mesulam syndrome
#27 progressive nonfluent aphasia
#28 binswanger disease
#29 binswanger encephalopathy
#30 leukoencephalopathy subcortical
#31 subcortical arteriosclerotic encephalopathy
#32 chronic progressive subcortical encephalopathy
#33 alcohol near amenstic
#34 alcohol near dysmnestic
#35 ethanol near (nervous system disorders)
#36 ethyl alcohol abuse neurologic syndromes
#37 lewy* bod* near disesase
#38 brain atrophy circumscribed lobar

#39 Pick* near disease
#40 cerebral amyloid angiopathy
#41 (neurofilament proteins) in DE,SU
#42 (tau proteins) in DE,SU
#43 (neurofibrillary tangles) in DE,SU
#44 (neuropil threads) in DE,SU
#45 (senile plaque*) in DE,SU
#46 (corticobasil ganglionic degeneration) or (cortical basal degeneration)
#47 cadisil or (cerebral autosomal dominant ischemia with subcortical leukoencephalopathy) (0 records)
#48 multisystems atrohpy (0 records)
#49 'Huntingtons-Disease' in DE (883 records)
#50 hydrocephalus normal pressure (140 records)
#51 'Creutzfeldt-Jakob-Syndrome' in DE (109 records)
#52 spongiform encephalopathy (39 records)
#53 cjd or jcd (80 records)
#54 Creutzfeldt-Jakob disease (183 records)
#55 explode 'Hypothyroidism-' in DE (260 records)
#56 explode 'Neurosyphilis-' in DE (39 records)
#57 vitamin B12 deficien* (50 records)
#58 frontotemporal lobar degeneration (15 records)
#59 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 (27527 records)
#60 #15 and #59 (338 records)
* #61 #60 and (LA=ENGLISH) and (PO=HUMAN) (322 records)

Appendix B

Forms

TREATMENT OF DEMENTIA - FULLTEXT SCREENING FORM

REF ID #	
FIRST AUTHOR	
SCREENER	

EXCLUDE ☐ because: **BUT……. KEEP ANYWAY as SPECIAL ☐**

1. ☐ **Language other than English (specify)** _____
2. ☐ **Not a full article …….. ☐ Should check for full article**
3. ☐ **No Dementia subjects in population**
4. ☐ **Not a treatment for Dementia**
5. ☐ **Dementia population not randomized to treatment**
6. ☐ **No outcomes provided for Dementia subjects**
7. ☐ **Other reason (specify)** _____

**** ☐ **** CONSULTATION REQUIRED

INCLUDE ☐ for the following interests:

☒ **Diagnosis of interest:** ☐ **Alzheimers** ☐ **AIDS dementia** ☐ **MCI** ☐ **CIND** ☐ **CLOND** ☐ **Aphasia** ☐ **Huntington's** ☐ **Parkinson's** ☐ **Alcohol** ☐ **Supranuclear Palsy** ☐ **Pick's** ☐ **Hypothyroidism** ☐ **Vitamin deficiency** ☐ **Vascular** ☐ **Corticobasal deterioration** ☐ **Lewy bodies** ☐ **Organic Brain**

(other) ☐ _____

☒ **Treatments randomized**

☐ **Placebo** ☐ **Tacrine** ☐ **Donepezil/Aricept** ☐ **Rivastigmine** ☐ **Acetylcholine/inhibitors** ☐ **Galantamine** ☐ **Metrifonate** ☐ **Memantine** ☐ **Ginko Bilboa** ☐ **Estrogens**

(specify others) _____

☒ **Population analyzed** ☐ **All** ☐ **Subgroup (specify)** _____

☒ **Outcomes reported (of randomized treatment on included population)** _____

_____

☒ **Other** _____

☐ **Include by consensus**
☐ **Exclude by consensus**

TREATMENT OF DEMENTIA – GUIDE TO FULLTEXT SCREENING FORM

USING THE FORM

a) Be sure to fill in the DM ID#, the Name of the First Author and Your Initials in the three boxes at the top right of the form.

b) If a paper should be excluded, fill in the "EXCLUDE" box and fill in the box for the reason for exclusion that occurs first in the list of 7 reasons for exclusion.

c) The boxes for "KEEP ANYWAY as SPECIAL' or "should check for full article" can also be checked if it is an excluded article but may be useful to our review as background or clarification of it appears to be a companion paper for another report that is likely in our review.

d) If you choose to exclude the paper, the details for included papers do not need to be filled in.

e) If a paper should be included, fill in the "INCLUDE" box and fill in the information for ONLY TWO of the subsequent categories listed: Diagnosis of interest and Treatments randomized. Ignore Population analyzed, Outcomes reported and Other…….we may use them later for grouping.

f) If you are not sure if a paper qualifies for inclusion and want it to be looked at by our clinicians or methodologists, mark "CONSULTATION REQUIRED"

g) If a paper is excluded because the Dementia population is not defined by DSM, NINCDS OR ICD-10 criteria, save it for consultation and mark "population' beside the Consultation Required box.

EXCLUDING ARTICLES

1. Complete report must be in English to be included. If there is only an English abstract, exclude the article.

2. Only full reports will be included. If the article is a letter, comment, editorial, news, abstract, proceedings of a meeting or any other brief description, exclude the article. If it seems that the study would otherwise be included, check the box "Should check for full article".

3. All dementia populations will be accepted at this stage if they are documented by DSM III, DSM III-R, DSM IV, NINCDS-ADRDA, ICD-9, ICD-10. The population studied may include those with mild cognitive impaired (MCI), cognitive impairment, not Dementia (CIND), cognitive loss, not Dementia (CLOND). If the author cites the article by McKhann as the criteria for diagnosis, it can be included because that is the criteria for NINCDS.

4. Articles included should look at treatment of disease, cognition, behaviour, or quality of life, time to deterioration, depression, falls etc. Exclude if outcomes reported are ONLY neurophysiologic or neuroimaging (eg EEG)

5. Exclude if not a report of a randomized controlled trial.

6. Outcomes reported should be for subjects with Dementia. If the entire population does not have Dementia, only data sub-grouped for Dementia will be examined. Exclude if there are no outcomes of interest reported for specifically Dementia subjects.

7. Any previously unmentioned, compelling reason to exclude the study should be specified.

INCLUDING ARTICLES

1. If you are unclear about whether the diagnosis is an included one, mark the referral box and pass along for a consult. If entire population is demented, mark boxes for all specific diagnoses included in study outcomes. If not all of population is demented, mark boxes for all specific diagnoses included in subgroup analysis of outcomes. If diagnosis is not listed as a choice, but is an included diagnosis, specify on line provided.

2. Specify treatments if they were randomly provided to the dementia population.

DETAIL ABOUT DISEASE TERMS (terms from the literature search)

NOT

- Not normal or healthy volunteers
- Not general population of elderly persons
- Not selected for depression (some may have dementia but not all)…BUT… If subgroup analysis may have been done, it should be marked "Retrieve".

INCLUDE

- Alzheimer's disease by DSM, NINCDS OR ICD
- Dementia defined by DSM, NINCDS OR ICD
- MCI – mild cognitive impairment
- CIND – cognitive impairment, not Dementia
- CLOND – cognitive loss, not Dementia

*Keep articles aside in a group if the intervention is directed toward the caregiver or caregiver/patient dyad.

TREATMENT OF DEMENTIA - FULLTEXT SCREENING FORM SECONDARY EXCLUSION

REF ID #	
FIRST AUTHOR	
SCREENER	

Article was included on first fulltext screening form

Crossover trials

Include ☐ there is data of interest to extract on first phase alone

Exclude ☐ there is no data of interest to extract on first phase alone

Quality for all trials included on primary screen

Any blinding was done ☐ **NO…..EXCLUDE**
☐ **YES…CONTINUE**

Withdrawals were enumerated for each arm ☐ **YES….INCLUDE**
☐ **NO …..EXCLUDE**

REFID _____ 1st AUTHOR _____ EXTRACTOR _____

QUALITY SCORE FOR JADAD SCALE AND FOR MODIFIED JADAD SCALE

CRITERIA	RESULT	SCORING	SCORE
Reported as randomized	☐ YES ☐ NO	1 point for YES	
Randomization is appropriate	☐ YES ☐ NO ☐ NOT DESCRIBED	1 point for YES -1 point for NO	
Double blinding is reported	☐ YES ☐ NO	1 point for YES	
Double blinding is appropriate	☐ YES ☐ NO ☐ NOT DESCRIBED	1 point for YES -1 point for NO	
Withdrawals are reported by number and reason per arm	☐ YES ☐ NO	1 point for YES	
JADAD SCORE			**/5**
Method used to assess adverse events is described	☐ YES ☐ NO	1 point for YES	
Methods of statistical analysis are described	☐ YES ☐ NO	1 point for YES	
Inclusion criteria reported	☐ YES ☐ NO	1 point for YES in at least one of two criteria	
Exclusion criteria reported	☐ YES ☐ NO		
JADAD IN AD SCORE			**/8**
Intended allocation to tx group concealed from investigator	☐ YES ☐ NO ☐ NOT REPORTED		

Table A. Key Characteristics

REF ID #	Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified by patient characteristic

GUIDE TO DATA EXTRACTION TABLE

REF ID #	Enter number written on top of first page of article.
Author / Year	Enter last name of first author on one line and year of publication on the second line.
Funding Source	Enter one of the following codes: IF (Industry Funded) PI (Partially funded by Industry) IS (Industry provided Supplies) NI (Non-Industry funding source) NR (not reported) Use more than one code if necessary.
Quality score	Enter the Modified Jadad score for Alzheimer's Disease (out of 8 points)
Interventions	Enter name of drugs used in trial. Use the most commonly recognized name (eg use Tacrine instead of generic name). If more than one drug is used, put one on each line. If a dose response trial is reported, treat as one drug at the highest dose. If placebo is used, enter as first drug.
Criteria for Diagnosis	Indicate what criteria were used for diagnosis. It should be one of NINCDS, DSMIII, DSMIII-R, DSMIV, ICD-10
Diagnosis	Enter all dementia diagnoses included in the trial.

PDD = PRIMARY DEGENERATIVE DEMENTIA
MID = MULTI- INFARCT DEMENTIA
AD = DAT = SDAT = ALZHEIMER'S DEMENTIA
MIXED
VaD = VASCULAR DEMENTIA
DEMENTIA

Disease Severity	Use the descriptive terms as used in the paper.
Total Number randomized	Give the number in all groups that were initially randomized.
Number completing trial	Give the number in all groups that completed the treatment. If ITT population is given, report also.
Mean age (range) % Male (M) Population	Enter whatever information is given in paper for whole population Compute this figure if possible for those randomized at baseline Give any special inclusion criteria (or existing factor in population) which may affect the external validity (eg comorbid disorders, race, setting)
Highest Dose	Give the dose per day. If the dose was titrated up to individual doses, give the highest dose used and enter details of titration on the second line. Record as reported in paper - make sure to note if dose is by weight or a set amount and report how often given (preferably by day).
Treatment Period open extension	This should be the length of time for which the subjects received drug treatment. Use the longest period if there is more than one. Note here if there is an
Outcomes Measured	List all of the tests reported. If a battery of psychological tests were done, list the name of the battery. If physical tests are reported (e.g. blood tests, scans) list in very general terms (e.g. blood levels, EEG).
Outcome reports stratified by patient characteristic	Enter a Y if any of the data is reported in any way and is stratified by any patient characteristic (e.g. gender, age, race, genotype, education) and describe what the characteristic is. Otherwise, enter N.

Table B. Evidence Results

DRUG

REF ID #	Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P value
				Baseline		**Mid-Point: (specify)**		**Final: (specify) 24w**	
				Baseline		**Mid-Point: (specify)**		**Final: (specify)**	

GUIDE TO DATA EXTRACTION TABLE B

REF ID #	Enter number written on top of first page of article.
Author / Year	Enter last name of first author on one line and year on the second line
Analysis groups and Interventions	Use one line for each intervention that will be reported on. Number them as follows (1] 2] 3]) Make the Control condition # 1 and Drug treatment conditions # 2 and so forth. If results are reported as change or relationship between baseline and later time-points or between placebo and drug conditions, these will be added as additional Analysis Groups (e.g. [3] Baseline vs 28w Placebo) would be entered as the third Analysis Group and would be for the score that reports the change in value between the one at baseline and the one at 28 weeks for the placebo group. The Analysis Group [5] Placebo vs Tacrine 28w) would be the fifth Analysis Group and be used for the score that reports the change in value between the placebo condition and the drug condition at 28 weeks. If subgroup analysis has been reported, an Analysis Group can be created to report the results. For Analysis Groups that refer to the drug used, enter the name of drug used in trial. Use the most commonly recognized name (eg use Tacrine instead of generic name). If more than one drug is used, put one on each line. If variable dosing is used within an arm, report the higher dose. Put the Placebo condition first in the list
Test Used	List all psychological and functional tests used that have extractable data (cognition, behavior, functional, global). Do not report on physiological measurements such as blood levels. Enter the primary outcomes first in the list and bold the font on the test name.
Baseline, Mid-Point, Final	Enter number of hours, days, weeks, months, years from baseline measurement to current measurement. Use abbreviations (h = hours, d = days, w = weeks, m = months, y = years) If more than 3 time points given, use the most central one for Time 2.
Result Values	Enter the value for Mean " Standard Deviation for each arm for each time-point for each test. If Standard Error is used, use an * . If % is used, enter the % sign after the value. If the test consists of subsections (eg a battery that also reports the total), just use the total score unless a sub-score is a primary outcome. Give P value if provided. If no P value available, but CI reported, put CI in P value column.

Overall Summary Table Interpretation:

SC = statistically significant CHANGE at the alpha = 0.05

= based on the PRIMARY outcomes (no need to specify as 1^{o} because this is the default). If the paper does not specify primary or secondary ASSUME primary for all reported outcomes

= report secondary outcomes ONLY when there is NO primary variable for that domain AND indicate with (2^{o}) in front of the result code

= based on the ITT analyses results ONLY; if ITT results were not reported in the paper, then indicate with an asterick (*) located behind the result code (i.e. NS*)

= this change is ONLY relative to placebo (within group findings are reported in Table B..so not necessary to recapitulate this in summary table)

= in those instances where there is A PRIORI hypotheses for subgroup analyses and there are statistical results reported, then indicate with a symbol (i.e. # or ^) that the subgroup analyses were SC or NS and specify with respect to what factor (i.e. Vascular dementia versus not, or gender, etc)

NS = not statistically significant effect for primary or secondary outcomes (some additional domains are tested with the secondary outcomes)

NT = outcomes were not tested reflecting in this domain

MX = mixed results for two primary outcomes (i.e one was significant and the other variable was not significant) and do not represent a SUBGROUP analysis

= indicates that two measures within the same domain show conflicting results (one outcome is significant and the other is not significant)

Reporting Safety information in Randomized controlled trials (Ioannidis and Lau, 2002)

DOMAIN recommendation **Ioannidis and Lau**	**OUR QUESTION**	**STATUS**
FREQUENCY of **WITHDRAWALS** due to adverse events (**AE**)	Do the authors specify the **number** of patients **withdrawn** from the study due to AE **per study arm** and **per type** of AE that caused withdrawal	Y N Unclear Y N Unclear
FREQUENCY of **AE** (can be stated as a count or as a proportion for either CLINICAL AE or LABORATORY-DEFINED TOXICITY)	Do the authors provide the **number of AE** with respect to **severity** (reference to a known scale of toxicity such as mild, moderate, severe, life threatening or grades 1 to 3, etc) **per study arm** and **per type** of **specific AE** (i.e. diarrhea, headache, etc)	Y N Unclear Y N Unclear
Was the recording of the AE (i.e. surveillance) **ACTIVE** or **PASSIVE**	Is the surveillance **ACTIVE** (actively monitor the presence of absence of AE during the study…do not rely on methods that are PASSIVE (sometimes called spontaneous reporting).	Y N Unclear
Describe a SCHEDULE for collection of safety info	**Optional** 1) Do the authors specify the **schedule for collection** of safety information?	
FREQUENCY of **SERIOUS** AE (i.e. results in death, requires inpatient hospitalization, persistent or significant disability or is life threatening, WHO 2001)	Are exact **numbers** for high-grade (**serious and life threatening**) clinical AE laboratory toxicity reported.	Y N Unclear
SEVERITY of **each** AE (i.e. mild, moderate, or severe headache)	Have **each** of the AE been reported with respect to a **severity continuum** (i.e. mild diarrhea, severe headache, etc**)** ? Have **some** of the AE been reported with respect to a **severity grade**?	Y N Unclear Optional: Y N Unclear
Description of **UNUSUAL** or **NOT PREVIOUSLY RECORDED** AE	Has a detailed description of cases of **unusual or not previously recorded** AE effects been presented?	Y N Unclear
STANDARDIZED SCALES used to capture AE.	Do the authors report the use of widely known, **standardized scales** for AE? **Specify scale:** If the scale is **new**, do the authors provide definitions for the grades of severity	Y N Unclear Optional: Y N Unclear
		Y N Unclear

Identify specific **SAFETY TESTS** or **QUESTIONNAIRES** used for data collection	Do the authors identify specific safety tests or questionnaires used for data collection	

THRESHOLD SCORING for ADVERSE EVENTS:

1) Scoring:

   YES = 1
   NO = 0
   Unclear = consult with other rater to reach consensus

2) For the first 3 questions a MINIMUM score of **3** is required to proceed to the subsequent **5** questions

3) If all patients were accounted for (i.e. no withdrawals), then we assume a score of 2 for the WITHDRAWAL due to AE question

4) If no mention of serious (see definition) is mentioned in the paper, then we will ASSUME that they were NOT monitored (rather than not reported)

Appendix C

Evidence tables

Guide to the Results Tables

The results from all of the studies have been recorded in the following tables, which have been organized according to the intervention used in the trial. There are three sections:

1) Cholinergic neurotransmitter modifying agents (CNMA)
2) Non-cholinergic neurotransmitter/neuropeptide modifying agents (NCNNM)
3) Other pharmacological agents (OTHER)

Within each category, the results for drugs with three or more trials included are grouped together and presented in alphabetical order by drug name. There is a table showing the characteristics of the all of the studies using the drug. This table is followed by a separate table for each of the studies using that drug which shows the detailed results reported. These detailed tables are followed by a table containing adverse event information about each of the studies using that particular drug. Where there are only one or two trials included which use a drug, the tables for these studies are grouped together as various in tables as described above.

Following is a list of all of the drugs found in this review and the section in which they can be found. The drugs are ordered alphabetically within their section.

INTERVENTION	DRUG GROUP
5'-MTHF (FOLATE)	OTHER
ALAPROCLATE	NCNNM
ALPRAZOLAM	NCNNM
AMITRIPTYLINE	OTHER
ANAPSOS	NCNNM
ANIRACETAM	CNMA
ANTAGONIC STRESS	CNMA
ATEROID	OTHER
BMT	OTHER
BMY (NOOTROPIC)	NCNNM
BUFLOMEDIL	OTHER
CARBAMAZEPINE	CNMA
CARNITINE	CNMA
CEREBROLYSIN	OTHER
CHOTO-SAN (HERB)	OTHER
CITALOPRAM	NCNNM
CITICOLINE	OTHER
CYCLANDELATE	OTHER
DENBUFYLLINE	OTHER
DESFERRIOXAMINE (DFO)	OTHER
DICLOFENAC/MISOPROSTOL	OTHER
DIPHENHYDRAMINE	NCNNM
DIVALPROEX	NCNNM
DONEPEZIL	CNMA
EPTASTIGMINE	CNMA
ERGOKRYPTINE DEK (DIHYDROERGOKRYPTINE)	OTHER

INTERVENTION	DRUG GROUP
ESTROGENS	OTHER
FLUOXETINE	NCNNM
FLUVOXAMINE	NCNNM
GALANTAMINE	CNMA
GINKO BILOBA	OTHER
GLYCOSAMINOGLYCAN POLYSULFATE	OTHER
GUANFACINE	OTHER
HALOPERIDOL	NCNNM
HUPERZINE-A	CNMA
HYDERGINE	OTHER
HYDROXYCHLOROQUINE	OTHER
IDEBENONE	OTHER
IMIPRAMINE	NCNNM
INDOMETHACIN	OTHER
LINOPIRIDINE	CNMA
LISURIDE	NCNNM
LORAZEPAM	NCNNM
LOXAPINE	NCNNM
LU25-109	NCNNM
MAPROTILINE	NCNNM
MECLOFENOXATE	CNMA
MELPERONE	NCNNM
MEMANTINE	NCNNM
METRIFONATE	CNMA
MIANSERIN	NCNNM
MINAPRINE	NCNNM
MOCLOBEMIDE	NCNNM
MONOSIALOTETRAHEXOSYLGANGLIOSIDE (GM1)	OTHER
N-ACETYLCYSTEINE NAC	OTHER
NAFTIDROFURYL	NCNNM
NICERGOLINE	CNMA
NIMESULIDE (NSAID)	OTHER
NIMODIPINE	OTHER
NIZATIDINE	OTHER
NOOTROPIC	OTHER
OLANZAPINE	NCNNM
ORG 2766	OTHER
OXAZEPAM (Benzodiazapine)	NCNNM
OXIRACETAM	OTHER
PAROXETINE	NCNNM
PENTOXYFYLLINE	OTHER
PERPHENAZINE	NCNNM
PHOSPHATIDYLSERINE	NCNNM
PHYSOSTIGMINE	CNMA
PIRACETAM	OTHER

INTERVENTION	DRUG GROUP
POSATIRELIN	CNMA
PREDNISONE	OTHER
PROPENTOFYLLINE	OTHER
PYRITINOL	OTHER
RISPERIDONE	NCNNM
RIVASTIGMINE	CNMA
SABELUZOLE	CNMA
SELEGILINE (DEPRENYL)	NCNNM
SERTRALINE	NCNNM
SIMVASTATIN	OTHER
SULFOMUCOPOLYSACCHARIDES	OTHER
SULODEXIDE	OTHER
TACRINE	CNMA
THIAMINE	OTHER
THIORIDAZINE	NCNNM
TIAPRIDE	NCNNM
TRAZODONE	NCNNM
VASOPRESSIN (DDAVP)	OTHER
VELNACRINE	CNMA
VINCAMINE	OTHER
VITAMIN E	OTHER
XANOMELINE	NCNNM
XANTINOLNICOTINATE	OTHER

Appendix D

Peer review

Peer Reviewers for the Treatment of Dementia Report

1. Dr. Sandra Black, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
2. Dr. Malaz Boustani, Indiana University School of Medicine, Indianapolis, Indiana, USA
3. Dr. Charles Cefalu (American Geriatrics Assoc)
4. Dr. Larry Chambers, University of Ottawa Institute for Health of the Elderly, Ottawa, Ontario, Canada
5. Dr. Tommy Cross (ACP/ASIM representative), Colorado Springs, Colorado, USA
6. Dr. Rachelle Doody, Baylor College of Medicine, Houston, Texas, USA
7. Dr. John Feightner, University of Western Ontario, Canadian Task Force for Periodic Health, London, Ontario, Canada
8. Dr. Serge Gauthier, Alzheimer's Disease Research Unit, McGill Centre for Studies in Aging, Verdun Quebec, Canada
9. Lisa Gwyther (American Geriatrics Assoc), MSW Duke University, Durham, North Carolina
10. Dr. David Hogan, Division of Geriatric Medicine, Calgary, Alberta, Canada
11. Dr. Rodney Hornbake, (ACP/ASIM representative), Hadlyme, Connecticut, USA
12. Dr. Roy Jones, St. Martin's Hospital, Bath, UK
13. Dr. David Royall, UTHSCSA, San Antonio Texas, USA
14. Dr. Lon Schneider (Cochrane), Keck School of Medicine, University of Southern California, Los Angeles, California
15. Dr. Jennie Ward-Robinson, US National Alzheimer's Association, Chicago, Illinois, USA
16. Dr. Peter Whitehouse (Cochrane), Case Western Reserve University, Cleveland, Ohio

Others reviewing the report:

Dr. Vincenza Snow – partner, ACSIM
Dr. Martin Kabongo - American Association of Family Practitioners
Dr. Marcel Morrison-Bogorad - Representative from the Institute for Aging (NIH)
David Atkins, Kate Rickard and AHRQ staff
Mary Grady – technical review (AHRQ)

Criticism Editor:

Dr. Patricia Huston, Ottawa, ON

Structured format for collecting referee comments

Thank you for agreeing to review this report. This is still in the draft stages and a thorough copy edit will take place before the publication of the final report. Please do not feel you need to spend your time correcting spelling and punctuation – we are relying on your expertise to address the questions below and provide insight that will assist us in improving the content and format of the report.

Problem Formulation

- Are review questions well formulated with specified key components?
- Are comparison groups clearly stated?
- Were major changes in review questions avoided during the review process?

Study Identification

- Is there a thorough search for relevant data using appropriate resources?
- Are there unbiased explicit searching strategies that are appropriately matched to the question?

Study Selection

- Are appropriate inclusion and exclusion criteria used to select articles?
- Are selection criteria applied in a manner that limits bias?
- Are efforts made to identified unpublished data, if this is appropriate?
- Are major changes in selection criteria avoided during the review process?
- Are reasons for excluding studies from the report stated?

Appraisal of Studies

- Is the validity of individual studies addressed in a reliable manner?
- Are important parameters (e.g., setting, study population, study design) that could affect study results systematically addressed?

Data Collection

- Is there a minimal amount of missing information regarding outcomes and other variables considered key to interpretation of results?
- Are efforts made to reduce bias in the data collection process?

Data Synthesis

- Are important parameters, such as study designs, considered in the synthesis?
- Are reasonable decisions made concerning whether and how to combine the data?
- Are results sensitive to changes in the way the analysis was done?
- Is precision of results reported?

Discussion

- Are limitations and inconsistencies of studies stated?
- Are limitations of the review process stated?
- Are review finding integrated within the context of relevant indirect evidence?
- Are implications for research discussed
- Are implications for practice discussed?

Conclusions

- Are conclusions supported by the data reviewed?
- Are plausible competing explanations of observed effects addressed?
- Is evidence appropriately interpreted as inconclusive (no evidence of effect) or as showing a particular strategy did not work (evidence of no effect)?
- Are important considerations for decision makers identified, including values and contextual factors that might influence decisions?
- Is a summary of pertinent findings provided?

Appendix E

Outcome measures

Appendix E. Outcome Measures

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
ABID	Agitated Behavior Inventory for Dementia	High	Behavior
ABS	Adaptive Behavior Scale	Low	Function
ABSR	Aggressive Behavior Scale Rating	High	Behavior
ACES	Agitation Calmness Evaluation Scale	Low	Behavior
ACPT	Auditory Continuous Performance Test		Specific cognitive test
ADAS-	Alzheimer's Disease Assessment Scale	High	Global assessment
ADAS-Cog	Cognitive Sections		General cognitive function
ADAS-Noncog	Non-Cognitive, behavioral section		Behavior
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical, Global Impression of Change	High	Global assessment
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living	Low	Function
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale	High	Function
ADL	Activities of Daily Living	High	Function
ADL-C	Activities of Daily Living Checklist		Function
ADL-PDS	Activities of Daily Living Progressive Deterioration Scale		Function
ADS	Alzheimer's Deficit Scale		Global assessment
AFBS	Aversive Feeding Behavior Scale	High	Behavior
AGS- E	Assessment of Global Symptomatology - Elderly		Global assessment
AIMS	Abnormal Involuntary Movement Scale	High	Adverse Events, Dyskinesia
AMTS	Abbreviated Mental Test Score		General cognitive function

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
---	Barbizet Visuospatial	Low	Specific cognitive test
BARS, BAS	Barnes Akathisia Rating Scale	High	Adverse Events, Akathisia
BDI	Beck Depression Inventory	High	Behavior
BEHAVE – AD	Behavioral Pathology in Alzheimer's Disease Rating Scale	High	Behavior
BCRS	Brief Cognitive Rating Scale	High	General cognitive function
Bf-S	Self assessment according to Zerssen and Möller		Global assessment
BGP	Behavioral Rating Scale for Geriatric Patients		Global assessment
BI	Barthel Index		Function
Blessed-D or BDRS	Blessed Dementia Rating Scale	High	Global assessment
BNT	Boston Naming Test	Low	Specific cognitive test
BPRS	Brief Psychiatric Rating Scale	High	Behavior
BRMS	Bech-Rafaelsen Mania Scale		Behavior
BRSD	Behavioral Rating Scale for Dementia		Behavior
BSR	Babcock Story Recall Test	Low	Specific cognitive test
BSRT	Buschke Selective Reminding Test	Low	Specific cognitive test
BSV	Buschke Sentence Verification		Specific cognitive test
BLM	Buschke Letter Matching		Specific cognitive test
BVR	Benton Visual Retention – Number Correct Benton Visual Retention – Errors		Specific cognitive test
CamCOG	Cambridge Cognitive Schedule		General cognitive function
CAPE	Clifton Assessment Procedures for the Elderly	Low	Global assessment
CASI	Cognitive Abilities Screening Instrument	Low	General cognitive function

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
CAUST	Canadian Utilization of Service Tracking questionnaire	---	Health-care utilization and work productivity
---	Category Fluency	Low	Specific cognitive test
CDR-NH CDR-SB	Clinical Dementia Rating – Nursing Home Version Clinical Dementia Rating-Sum of Boxes	High	Global assessment
CDT	Clock Drawing Test		Specific cognitive test
CERAD-BRSD	Consortium to Establish a Registry for Alzheimer's Disease – Behavioral Rating Scale for Dementia	High	Behavior
CETM	---	---	General cognitive function
CCASSS	Computerized Cognitive Assessment System Speed Score / unweighted sum of reaction time	Low	Specific cognitive test
CATS	Caregivers' Activity Time Survey		Caregiver burden
CGAE	Clinical Global Assessment and Efficacy		Global assessment
CGI	Clinical Global Impression	High	Global assessment
CGIC	Clinical Global Impression of Change	High	Global assessment
CGRS	Clinician's Global Rating Scale		Global assessment
CIBIC	Clinician's Interview Based Impression of Change	High	Global assessment
CIBIC+	Clinician's Interview Based Impression of Change plus Caregiver	High	Global assessment
CDT	Clock Drawing Test	Low	Specific cognitive test
CMAI	Cohen Mansfield Agitation Inventory	High	Behavior
CNTB	Computerized Neuropsychological test battery		Specific cognitive test
COWAT	Controlled Oral Word Association Test	Low	Specific cognitive test
CS or CSDD	Cornell Scale for Depression in Dementia	NR	Behavior
CSS	Caregiver Stress Scale	High	Caregiver burden

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
CSI	University of Iowa Caregiver Stress Inventory		Caregiver burden
CVLT	California Verbal Learning Test		Specific cognitive test
---	Dependency Scale	High	Function
DAD	Disability Assessment for Dementia	Low	Function
DST	Digit Span Test		Specific cognitive test
DBDS	Dementia Behavioral Disturbance Scale		Global assessment
DMR	Dementia Questionnaire for Mentally Retarded Persons	High	Global assessment
DRS	Dementia Rating Scale	High	Global assessment
DSCS	Depressive Symptoms Collateral Source Cornell Scale		Behavior
DSS	Depressive Signs Scale	High	Behavior
DSST	Digit Symbol Substitution Test	Low	Specific cognitive test
EIS	Efficacy Index Score		Global assessment
EFRT	Emotional Face Recognition Test	Low	Specific cognitive test
ERP	Event-Related Potential (Amplitude)	Low	Response to stimuli
ESRS	Extrapyramidal Symptom Rating Scale	High	Adverse events/ Extrapyramidal symptoms
---	Facial Behavior	NR	Behavior
---	Finger Tapping Test	Low	Motor coordination
FAST	Functional Assessment Staging	High	Function
FCCA	Final Comprehensive Consensus Assessment		Global assessment
FCMT	Figure Copy/ Memory Test	Low	Specific cognitive test
FIGT	Figure detection test		Specific cognitive test

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
FIM	Functional Independence Measure	Low	Function
FOM	Fuld-Object Memory Evaluation		Specific cognitive test
FRS	Functional Rating Scale test	Low	Global assessment
GAGS	Guide to Adult Assessment Battery for Physical pharmacology		Specific cognitive test
GERRI	Geriatric Evaluation by Relative's Rating Instrument	High	Global assessment
GBS	Gottfries-Bråne-Steen Total Score Motor function subscale Intellectual subscale Emotional function subscale Symptoms subscale	High	Global assessment Function General cognitive function Behavior Behavior
GDS	Global Deterioration Scale	High	Global assessment
GIS	Global Impairment Scale (Adaptation of the CGIS)		Global assessment
GPI-E	General Psychiatric Impression – Elderly		Global assessment
GS	Gestalt Scale	High	Behavior
---	Grooved Pegboard Test	Low	Specific cognitive test
HAM-A	Hamilton Anxiety Scale	High	Behavior
HAM-D HDRS	Hamilton Rating Scale for Depression	High	Behavior
HDS	Hachinski Dementia Scale		Global assessment
HDS-R	Hasegawa's Dementia Scale – Revised		Behavior
HIS	Hachinski Ischemic Score	High	Global assessment
IADL	Instrumental Activities of Daily Living	High	Function
IDDD	Interview for Deterioration in Daily Living Activities in Dementia – complex task	High	Function
IPSC-E	Raskin's and Crook's Inventory of Psychic and Somatic Complaints for the Elderly	High	Behavior
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly	High	General cognitive function

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
---	Letter Cancellation	Low	Specific cognitive test
---	Letter Fluency	Low	Specific cognitive test
LMT	Logical Memory Test	Low	Specific cognitive test
LNNB	Luria-Nebraska Neuropsychological Battery		Specific cognitive test
LPRS	London Psychogeriatric Rating Scale		Behavior
MAACL-R	Multiple Affect Adjective Checklist-Revised	High	Behavior
MADRS	Montgomery-Asberg Depression Rating Scale	High	Behavior
MAE	Benton Multi-Lingual Aphasia Examination		Specific cognitive test
MCPT	Modified Continuous Performance Test		General cognitive function
MEMT	Memory test		Specific cognitive test
MMSE MMMSE SMMSE CMMSE	Mini-Mental Status Exam Modified MMSE Standardized MMSE Cantonese MMSE	Low	General cognitive function
MNLT	Modified Names Learning test		Specific Cognitive Test
MOSES			Behavior
MQ	Memory Quotient		General cognitive function
NAA	Scale from the Nuremberg Gerontopsychological inventory for assessing activities of daily living		Function
NAB	Nürnberg Alters-Beobachtungskala		Behavior
NAI	Nuremburg Age Inventory	Low	Function
NCT	Number Correction Test		Specific cognitive test

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
NDT	New Dot Test	Low	Specific cognitive test
NLT	Names Learning Test		Specific cognitive test
NMIC	Newcastle Memory, Information, and Concentration Test	Low	Specific cognitive test
NMS	Nowlis Mood Scale	High	Behavior
NOSGER	Nurses Observation Scale for Geriatric Patients	High	Global assessment
NOSGER-IADL	Nurses Observation Scale for Geriatric Patients – Instrumental Activities of Daily Living subscale	High	Function
NOSIE	Nurses Observation Scale for Inpatients	High	Global assessment
NPI (NPI-4, NPI-10)	Neuropsychiatric Inventory Subscores 4,10	Low	Behavior
NPI-NH	Neuropsychiatric Inventory – Nursing Home Version	High	Behavior
NSL			Behavior
NST	Number Symbol Test		Specific cognitive test
OARS – ADL	Older Americans Resource Scale	High	Function
OAS	Overt Aggression Scale		Behavior
OLT	Object Learning Test		Specific cognitive test
PANSS-EC	Positive and Negative Syndrome Scale		Behavior
PDRS	Psychogeriatric Dependency Rating Scale		Global assessment
PDS	Progressive Deterioration Scale	High	Function
PGIR	Patient's Global Improvement Rating		Global assessment
POMS	Profile of Mood States		Behavior
PSMS	Physical Self-Maintenance Scale	High	Function
PSQI	Pittsburgh Sleep Quality Index	High	Function

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
QoL	Quality of Life	Low	Function
QoL-P QoL-C	Patient-rated Quality of Life Caregiver-rated Quality of Life	Low	Function
RAGS	Relative's Assessment of Global Symptomatology		Global assessment
R-AVL	Rey Auditory-Verbal-Learning test	Low	Specific cognitive test
RGRS	Relatives' Global Rating Scale		Global assessment
RM RPM	Raven Matrices Raven's Progressive Matrices		Specific cognitive test
RMT	Randt Memory Test	Low	General cognitive function
RMBPC	Revised Memory and Behavior Problems Checklist	High	Behavior
RPT	Rivermead Profile Test		Behavior
RVM	Rey's Verbal Memory	Low	General cognitive function
SAS	Simpson-Angus Scale	High	Adverse effects, Extra-pyramidal symptoms
SAS-G	Self Assessment – Geriatric	High	Global assessment
	Snodgrass Picture Naming Task		Specific cognitive test
SBI	Spontaneous Behavior Interview		Behavior
SCAG	Sandoz Clinical Assessment – Geriatric	High	Global assessment
SCB	Screen for Caregiver Burden	NR	Caregiver burden
SCWIT	Stroop Color Word Interference Test		Specific cognitive test
	Set Test		Specific cognitive test
SF-36	Medical Outcomes Study Short-Form 36-Item Health Survey	Low	Function
SGRS	Stockton Geriatric Rating Scale	High	Global assessment
SHGRT	Stuard Hospital Geriatric Rating Scale		Behavior

Acronym/ Abbreviation	Test name	Level of Impairment with higher score	Domain
SKT	Syndrome Kurztest; Syndrome Short Test	High	Specific cognitive test
SIB	Severe Impairment Battery	Low	General cognitive function
SIP	Sickness Impact Profile		Function
SMQ	Squire's Memory Questionnaire		General cognitive function
SMST	Sternberg Memory Scanning	Low	General cognitive function
SRT-DR	Selective Reminding Procedure – delayed recall		Specific cognitive test
SRT SRT-Anxiety SRT-Depression	Kellner and Sheffield Rating Test		Behavior
SWFT	Semantic Word Fluency Test	---	Specific cognitive test
	Time to functional decline		Function
TK	Token Test	Low	Specific cognitive test
TP TPAT	Toulouse Piéron Toulouse Piéron Attention Test	Low	General cognitive function
TMT	Trail Making Test		Specific cognitive test
TSI	Test for Severe Impairment		Global assessment
UPDRS	Unified Parkinson's Disease Rating Scale	High	Adverse effects, Extrapyramidal symptoms
VHB	Video-recorder home-behavioral assessment		Behavior
VRGI	Video Rating of Global Impression		Global assessment
WAIS	Wechsler Adult Intelligence Scale (Verbal and Memory Performance scales)	Low	General cognitive function
WMS (MQ)	Memory Learning Restauration		Specific cognitive test
WMS-RR	Wechsley Memory Scale – Russel Revised		Specific cognitive test
ZVT ZVTG	Zahlen-Verbindungs Test – Trail Making Test	High	Specific cognitive test

Appendix F

List of excluded studies

Appendix F. List of excluded studies

Aarsland D, Larsen JP, Lim NG, et al. Olanzapine for psychosis in patients with Parkinson's disease with and without dementia. J Neuropsychiatry Clin Neurosci 1999; 11(3):392-4.
Status: *Not included because dementia population not randomized to treatment*

Aarsland D, Laake K, Larsen JP, et al. Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. J Neurol Neurosurg Psychiatry 2002; 72(6):708-12.
Status: *Cross-over trial;*

Aarsland D. Erratum: Donepezil for cognitive impairment in Parkinson's disease. A randomised controlled study. J Neurol Neurosurg Psychiatry 2002; 73(3):354.
Status: *Not included because not a full article*

Abalan F, Manciet G, Dartigues JF, et al. Nutrition and SDAT. Biol Psychiatry 1992 Jan 1; 31(1):103-5.
Status: *Not included because not a full article*

Abuzzahab FS, Sr., Merwin GE, Zimmermann RL, et al. A double-blind investigation of piracetam (nootropil) versus placebo in the memory of geriatric inpatients. Psychopharmacol Bull 1978 Jan; 14(1):23-5.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Abyad A. Prevalence of vitamin B12 deficiency among demented patients and cognitive recovery with cobalamin replacement. J Nutr Health Aging 2002; 6(4):254-60.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*
Adler LA, Peselow E, Rosenthal M, et al. A controlled comparison of the effects of propranolol, benztropine, and placebo on akathisia: An interim analysis. Psychopharmacol Bull 1993; 29(2):283-6.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Aerssens J, Raeymaekers P, Lilienfeld S, et al. APOE genotype: no influence on galantamine treatment efficacy nor on rate of decline in Alzheimer's disease. Dement Geriatr Cogn Disord 2001 Mar; 12(2):69-77.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Agnoli A, Martucci N, Manna V, et al. Effect of cholinergic and anticholinergic drugs on short-term memory in Alzheimer's dementia: a neuropsychological and computerized electroencephalographic study. Clin Neuropharmacol 1983; 6(4):311-23.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Agnoli A, Martucci N, Manna V. Quantitative EEG as a tool in neuropharmacological studies: The effect of naftidrofuryl in chronic cerebrovascular diseases (C.C.V.D.). Curr Ther Res Clin Exp 1985; 37(3):387-97.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Agnoli A, Manna V, Martucci N, et al. Randomized double-blind study of flunarizine versus placebo in patients with chronic cerebrovascular disorders. Int J Clin Pharmacol Res 1988; 8(3):189-97.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Aguglia E, Caraceni T, Genitrini S, et al. Comparison of teniloxazine and piracetam in Alzheimer-type or vascular dementia. Curr Ther Res Clin Exp 1995; 56(3):250-7.
Status: *Not included because Jadad Quality Scale score less than three*

Ahlin A, Nyback H, Junthe T, et al. THA in Alzheimer's dementia clinical biochemical and pharmacokinetic findings. Alzheimer's disease basic mechanisms diagnosis and therapeutic strategies 1990; 621-5.
Status: *Not included because not a full article*

Ahlin A, Nyback H, Junthe T, et al. Tetrahydroaminoacridine in Alzheimer's dementia: Clinical and biochemical results of a double-blind crossover trial. Hum Psychopharmacol 1991; (2):109-18.
Status : *Cross-over trial;*

Ahlin A, Hassan M, Junthe T, et al. Tacrine in Alzheimer's disease: Pharmacokinetic and clinical comparison of oral and rectal administration. Int

Clin Psychopharmacol 1994; 9(4):263-70.
Status: *Cross-over trial;*

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Status: *Not included because not a full article*

Aisen PS, Marin DB, Brickman AM, et al. Pilot tolerability studies of hydroxychloroquine and colchicine in Alzheimer disease. Alzheimer Dis Assoc Disord 2001 Apr; 15(2):96-101.
Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because no extractable data relevant to review*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Alexopoulos GS, Meyers BS, Young RC, et al. Executive dysfunction and long-term outcomes of geriatric depression. Arch Gen Psychiatry 2000 Mar; 57(3):285-90.
Status: *Not included because does not meet criteria for treatment for dementia patients*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Allain H, Neuman E, Malbezin M, et al. Bridging study of S12024 in 53 in-patients with Alzheimer's disease. J Am Geriatr Soc 1997; 45(1):125-6.
Status: *Not included because not a full article*

Almkvist O, Jelic V, Amberla K, et al. Responder characteristics to a single oral dose of cholinesterase inhibitor: A double-blind placebo-controlled study with tacrine in Alzheimer patients. Dement Geriatr Cogn Disord 2001 Jan; 12(1):22-32.
Status: *Cross-over trial;*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Altman H, Mehta D, Evenson RC, et al. Behavioral effects of drug therapy on psychogeriatric inpatients. I. Chlorpromazine and thioridazine. J Am Geriatr Soc 1973 Jun; 21(6):241-8.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Alvarez XA, Laredo M, Corzo D, et al. Citicoline improves memory performance in elderly subjects. Methods & Findings in Experimental & Clinical Pharmacology 1997 Apr; 19(3):201-10.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because Jadad Quality Scale score less than three*

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Status: *Not included because not a full article*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Ancoli-Israel S, Martin JL, Kripke DF, et al. Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. J Am Geriatr Soc 2002; 50(2):282-9.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because no extractable data relevant to review*

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Status: *Not included because not a full article*

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Status: *Not included because not a full article*

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Status : *Not included because not a full article*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because not a full article*

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Status: *Not included because not a full article*

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Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Ashford JW, Soldinger S, Schaeffer J, et al. Physostigmine and its effect on six patients with dementia. Am J Psychiatry 1981; 138(6):829-30.
Status: *Not included because dementia population not randomized to treatment*

Asthana S, Raffaele KC, Berardi A, et al. Treatment of Alzheimer's disease by continuous intravenous infusion of physostigmine. Alzheimer Dis Assoc Disord 1995; 9(4):223-32.
Status: *Cross-over trial;*

Asthana S, Greig NH, Holloway HW, et al. Clinical pharmacokinetics of arecoline in subjects with Alzheimer's disease. Clin Pharmacol Ther 1996 Sep; 60(3):276-82.
Status: *Not included because no extractable data relevant to review*

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Status: *Cross-over trial;*

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Status: *Not included because Jadad Quality Scale score less than three*

Ather SA, Shaw SH, Stoker MJ. A comparison of chlormethiazole and thioridazine in agitated confusional states of the elderly. Acta Psychiatr Scand 1986; 73(Suppl 329):81-91.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Auer SR, Monteiro IM, Reisberg B. Behavioral symptoms in dementia: community-based research. Int Psychogeriatr 1996; 8(Suppl 3):363-6, 381, 382.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Avorn J, Soumerai SB, Everitt DE, et al. A randomized trial of a program to reduce the use of psychoactive drugs in nursing homes. N Engl J Med 1992 Jul 16; 327(3):168-73.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Avorn J, Benner J, Ford I, et al. Measuring the cost-effectiveness of lipid-lowering drugs in the elderly: The outcomes research and economic analysis components of the PROSPER trial. Control Clin Trials 2002; 23(6):757-73.

Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not randomized to treatment*

Bach D, Bach M, Bohmer F, et al. Reactivating occupational therapy: A method to improve cognitive performance in geriatric patients. Age Ageing 1995 May; 24(3):222-6.
Status: *Not included because does not meet criteria for treatment for dementia patients*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wesensten NJ, Balkin TJ, Belenky GL. Effects of daytime administration of zolpidem versus triazolam on memory. Eur J Clin Pharmacol 1995; 48(2):115-22.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wesnes K, Simmons D, Rook M, et al. A double-blind placebo-controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. Hum Psychopharmacol 1987; 2:159-69.
Status : *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wesnes KA, McKeith IG, Ferrara R, et al. Effects of rivastigmine on cognitive function in dementia with lewy bodies: A randomised placebo-controlled international study using the cognitive drug research computerised assessment system. Dement Geriatr Cogn Disord 2002; 13(3):183-92.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wettstein A, Spiegel R. Clinical trial with the cholinergic drug RS 86 in Alzheimer's disease (AD) and senile dementia of the Alzheimer type (SDAT). Psychopharmacologia 1984; 84(4):572-3.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

White CM, Dicks RS. Rivastigmine: An acetylcholinesterase inhibitor for patients with Alzheimer's disease. Hosp Formul 1999; 34(6):493-9.
Status: *Not included because dementia population not randomized to treatment*

White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacologia 1999 Apr; 143(2):158-65.
Status: *Cross-over trial;*

White JC, Christensen JF, Singer CM. Methylphenidate as a treatment for depression in acquired immunodeficiency syndrome: an n-of-1 trial. J Clin Psychiatry 1992 May; 53(5):153-6.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

White L, Crovello JN, Rosenberg SN, et al. Evaluation of isobaric oxygenation for the aged with cognitive impairment: Pilot study. J Am Geriatr Soc 1975 Feb; 23(2):80-5.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because does not meet criteria for treatment for dementia patients*

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Status: *Not included because does not meet criteria for treatment for dementia patients*

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Status: *Not included because dementia population not randomized to treatment*

Wilcock GK, Scott M, Pearsall T, et al. Galanthamine and the treatment of Alzheimer's disease. Int J Geriatr Psychiatry 1993; 8(9):781-2.
Status: *Not included because not a full article*

Wilcock GK, Surmon DJ, Scott M, et al. An evaluation of the efficacy and safety of tetrahydroaminoacridine (THA) without lecithin in the treatment of Alzheimer's disease. Age Ageing 1993; 22(5):316-24.
Status: *Cross-over trial;*

Wilkinson D, Srikumar S, Shaw K, et al. Drama and movement therapy in dementia: A pilot study. Arts in Psychotherapy 1998; (3):195-201.
Status: *Not included because dementia population not randomized to treatment*

Wilkinson D. Clinical experience with Donepezil (Aricept) in the UK. J Neural Transm Suppl 1998; 54:311-5.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Pract 2002 Sep; 56(7):509-14.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because Jadad Quality Scale score less than three*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Willis SL, Schaie KW. Training the elderly on the ability factors of spatial orientation and inductive reasoning. Psychol Aging 1986 Sep; 1(3):239-47.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wilson AL, Langley LK, Monley J, et al. Nicotine patches in Alzheimer's disease: Pilot study on learning, memory, and safety. Pharmacol Biochem Behav ; 51(2-3):509-3.
Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because dementia population not randomized to treatment*

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Status : *Not included because dementia population not randomized to treatment*

Winther K, Randlov C, Rein E, et al. Effects of Ginkgo biloba extract on cognitive function and blood pressure in elderly subjects. Curr Ther Res Clin Exp 1998; 59(12):881-8.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because does not meet criteria for treatment for dementia patients*

Wolfgang SA. Olanzapine in whole, not half, tablets for psychosis from Alzheimer's dementia. Am J Health Syst Pharm 1999 Nov 1; 56(21):2245-6.
Status: *Not included because not a full article*

Wolters EC, Riekkinen P, Lowenthal A, et al. DGAVP (Org 5667) in early Alzheimer's disease patients: An international double-blind, placebo-controlled, multicenter trial. Neurology 1990 Jul; 40(7):1099-101.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wong YT, Packer H. Penicillin versus penicillin-malaria in the treatment of dementia paralytica. Br J Vener Dis 2000; 25(1):39.
Status: *Not included because not a full article*

Woods B. Promoting well-being and independence for people with dementia. Int J Geriatr Psychiatry 1999; 14(2):97-109.
Status: *Not included because dementia population not randomized to treatment*

Wooltorton E. Risperidone (Risperdal): Increased rate of cerebrovascular events in dementia trials. CMAJ 2002 Nov 26; 167(11):1269-70.
Status: *Not included because not a full article*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Wright LK, Litaker M, Laraia MT, et al. Continuum of care for Alzheimer's disease: A nurse education and counseling program. Issues Ment Health Nurs 2001 Apr; 22(3):231-52.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Wroblewski T, Silvestre J, Castaner J. JTP-4819. Cognition enhancer, prolyl endopeptidase inhibitor. Drugs of the Future 1998; 23(4):384-9.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Xu H, Shao N, Cui D, et al. A clinical study of yi zhi capsules in prevention of vascular dementia.

J Tradit Chin Med 2000 Mar; 20(1):10-3.
Status: *Not included because Jadad Quality Scale score less than three*

Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. N Engl J Med 2001 Apr 19; 344(16):1207-13.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

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Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yehuda S, Rabinovtz S, Carasso RL, et al. Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life. Int J Neurosci 1996 Nov; 87(3-4):141-4.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yesavage JA, Hollister LE, Burian E. Dihydroergotoxine: 6-mg versus 3-mg dosage in the treatment of senile dementia. Preliminary report. J Am Geriatr Soc 1979 Feb; 27(2):80-2.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Yesavage JA, Westphal J, Rush L. Senile dementia: Combined pharmacologic and psychologic treatment. J Am Geriatr Soc 1981; 29(4):164-71.
Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because dementia population not randomized to treatment*

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Status: *Not included because not a full article*

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Status: *Not included because dementia population not randomized to treatment*

Zank S, Schacke C. Evaluation of geriatric day care units: effects on patients and caregivers. J Gerontol B Psychol Sci Soc Sci 2002 Jul; 57(4):348-57.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zappoli R, Arnetoli G, Paganini M, et al. Contingent negative variation and reaction time in patients with presenile idiopathic cognitive decline and presenile Alzheimer-type dementia. Preliminary report on long-term nicergoline treatment. Neuropsychobiology 1987; 18(3):149-54.
Status: *Not included because Jadad Quality Scale score less than three*

Zappoli R, Arnetoli G, Paganini M, et al. Topographic bit-mapped event-related neurocognitive potentials and clinical status in patients with primary presenile mental decline chronically treated with nicergoline. Curr Ther Res Clin Exp 1991; 49(6):1078-97.
Status: *Not included because Jadad Quality Scale score less than three*

Zarit SH, Zarit JM, Reever KE. Memory training for severe memory loss: Effects on senile dementia patients and their families. Gerontologist 1982; 22(4):373-7.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zemlan FP, Keys M, Richter RW, et al. Double-blind placebo-controlled study of velnacrine in Alzheimer's disease. Life Sci 1996; 58(21):1823-32.
Status: *Not included because Jadad Quality Scale score less than three*

Ziemba C, Foster G, Neufeld R, et al. Haloperidol holiday: Is it a beneficial vacation for some nursing home residents? Clin Gerontol 1997; 17(3):15-24.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Zill P, Burger K, Behrens S, et al. Polymorphisms in the alpha-2 macroglobulin gene in psychogeriatric patients. Neurosci Lett 2000 Nov 17; 294(2):69-72.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zimmer JG, Eggert GM, Chiverton P. Individual versus team case management in optimizing community care for chronically ill patients with dementia. J Aging Health 1990; 2(3):357-72.
Status: *Not included because does not meet criteria for treatment for dementia patients*

Zisselman MH, Rovner BW, Shmuely Y, et al. A pet therapy intervention with geriatric psychiatry inpatients. Am J Occup Ther 1996 Jan; 50(1):47-51.
Status: *Not included because no extractable data relevant to review*

Zissis NP, Alevizos V, Dontas AS. Flunarizine, an inhibitor of Casup +sup 2-induced vascular constriction in geriatric patients. Curr Ther Res Clin Exp 1991; 29(3I):395-400.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. Neurology 2001 Oct 9; 57(7):1239-47.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

Zwerling I, Plutchik R, Hotz M, et al. Effects of a procaine preparation (Gerovital H3) in hospitalized geriatric patients: A double-blind study. J Am Geriatr Soc 1975 Aug; 23(8):355-9.
Status: *Not included because dementia population not defined by DSM, NINCDS or ICD*

EvTable1. Key characteristics: Carnitine (ALCAR).

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Livingston 1991	IF IS	5	Placebo Acetyl-L-Carnitine	NINCDS	AD	Probable or Possible	71	40	72.8y (65-80y) 18%M	NR	24w	ADL CGI Drawing KOLT MMSE MNLT NART PADL Recognition memory for words and pictures Word Fluency	No
Rai 1990	IS	7	Placebo Acetyl-L-Carnitine	NINCDS	AD	Mild-Mod	36	20	79y (> 60y) 38%M	2 g/d (1 g bid)	24w	ADL CGA Computerized psychometric tests DCT Digit Span GDS GMS-A HMII NART NLT OLT P300 Reisberg GDS Word Fluency Test	No

EvTable1. Key characteristics: Carnitine (ALCAR) cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Sano 1992	PI IS	6	Placebo Acetyl-L-Carnitine	NINCDS	AD	Mild-Mod	30	27	Mean NR (60-80y) %M NR Community	12 w 2500 mg/d and 12 w 3000 mg/d	24w	Benton Visual Retention test Cancellations CGI Digit span mMMSE SIP SMQ BSRT Verbal Fluency Wechsler memory scale	MMSE
Spagnoli 1991	PI	7	Placebo Acetyl-L-Carnitine	DSM III	AD	Mild-Mod	130	108	75.2y (>40y) 29%M 60.8% Community 39.3% Institution	2 g/d	1y	Blessed Dementia Scale Blessed Information Memory Concentration test Block-tapping test Finger agnosia test Geometrical constructive apraxia test Ideomotor and buccofacial apraxia Prose memory test Raven's matrices SBI Supra-span verbal learning Token test Verbal judgement and mental calculation test Visual search on matrices of digits Word association test	No

EvTable1. Key characteristics: Carnitine (ALCAR) cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Thal 2000a	IF	6	Placebo Acetyl-L-Carnitine	NINCDS	AD	Probable	227	167	59y (46-65y) 53%M 90% White	1 g tid	1y	ADAS-Cog ADAS-Noncog ADL CDR CIBIC MMSE	No
Thal 1996a Auxiliary Brooks 1998	IF	6	Placebo Acetyl-L-Carnitine	NINCDS DSM-III-R	AD	Mild-Mod	431	355	72y (NR) 44%M 93.5% White	1 g tid	12m	ADAS –Noncog ADAS-Cog ADL CDR-S CGI-C CGI-S IADL MMSE	Age

EvTable2. Study results: Carnitine (ALCAR).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: 12w**		**Final: 24w**	
Livingston, 1991	OC Analysis 1] Placebo 2] ALCAR (dose not specified) 3] Placebo Change from baseline 4] ALCAR change from baseline 5] Difference between placebo and ALCAR in change from baseline	ADL Clock Drawing Word fluency MMSE MNLT Object Learning RM – pictures RM – words	1] 34.9 2] 33.0 1] 5.66 2] 7.68 1] 16.6 2] 18.2 1] 16.1 2] 15.8 1] 20.9 2] 18.4 1] 12.3 2] 12.1 1] 14.5 2] 13.5 1] 15.2 2] 13.3		1] 31.5 2] 33.6 1] 5.63 2] 8.14 1] 14.7 2] 15.7 1] 15.3 2] 16.0 1] 21.1 2] 21.6 1] 11.0 2] 14.6 1] 14.6 2] 14.2 1] 14.2 2] 14.8	3] < 0.01 4] NS 5] NS 3] NS 4] NS 5] NS 3] <0.05 4] <0.05 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] <0.05 4] NS 5] NS	1] 32.3 2] 34.5 1] 5.22 2] 8.74 1] 15.3 2] 17.4 1] 15.1 2] 17.6 1] 21.9 2] 22.2 1] 13.1 2] 14.1 1] 15.2 2] 15.1 1] 13.8 2] 15.5	3] < 0.05 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] <0.01 4] NS 5] < 0.01

EvTable3. Study results: Carnitine (ALCAR).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 12w		Final: (specify) 24w	
Rai, 1990	OC Population 1] Placebo change from baseline 2] ALCAR 1g bid change from baseline 3] Placebo vs. ALCAR difference from baseline	GDS			1] 1.00 2] 0.25	1] NS 2] NS 3] NS	1] 2.00 2] 1.00	1] NS 2] NS 3] NS
		NLT			1] -3.38 2] 1.44	1] NS 2] NS 3] NS	1] –1.31 2] 0.57	1] NS 2] NS 3] NS
		Word Fluency Test			1] -1.00 2] -2.56	1] NS 2] NS 3] NS	1] –0.15 2] 0.57	1] NS 2] NS 3] NS
		ADL			1] 0.31 2] 0.22	1] NS 2] NS 3] NS	1] 0.15 2] 0	1] NS 2] NS 3] NS
		Digit Span			1] 0 2] 0.14	1] NS 2] NS 3] NS	1] –0.08 2] 0	1] NS 2] NS 3] NS
		Kendrick Battery Tests – Digit Copying Test			1] –4.25 2] 0.14	1] NS 2] NS 3] NS	1] –0.42 2] –1.00	1] NS 2] NS 3] NS
		Kendrick Battery Tests – Object Learning Test			1] 2.69 2] 1.00	1] NS 2] NS 3] NS	1] 1.77 2] –0.86	1] NS 2] NS 3] NS
		Clinical Global Improvement					1] 3.92 2] 3.6	3] NS
		Efficacy Index					1] 12.0 2] 10.29	3] NS

EvTable4. Study results: Carnitine (ALCAR).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 24 w**	
Sano 1992	OC Analysis 1] Placebo 2] ALCAR 2500 mg/d for 3m 3000mg/d for 6m 3] Difference between Placebo and ALCAR in change from baseline	SRT total recall WMS WMS Paired Associates mMMSE SIP SMQ Other Neuropsychological Tests	1] 21.4 (7.6) 2] 22.1 (7.3) 1] 2.9 (1.6) 2] 2.8 (1.8) 1] 6.3 (1.4) 2] 7.0 (2.0) 1] 35.3 (7.2) 2] 35.5 (5.4) 1] 27.3 (15.6) 2] 25.5 (12.5) 1] 38.7 (8.5) 4] 38.5 (8.3)				1] 16.0 (10.0) 2] 21.2 (8.8) 1] 2.2 (2.1) 2] 3.0 (1.6) 1] 6.4 (3.9) 2] 6.5 (1.9) 1] 32.4 (9.3) 2] 34.3 (6.3) 1] 24.17 (16.5) 2] 22.9 (12.5) 1] 45.1 (10.8) 2] 45.0 (8.8)	3] NS 3] NS 3] NS 3] NS 3] NS 3] NS 3] NS

EvTable5. Study results: Carnitine (ALCAR).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: 12m**	
Spagnoli, 1991	ITT Population 1] Placebo 2] ALCAR 250mg/bid 3] Difference between placebo and ALCAR 4] Difference between placebo and ALCAR in change from baseline	BDS	1] 9.5 (3.8) 2] 9.4 (4.3)	3] 0.84			1] 13.0 (4.6) 2] 11.0 (5.3)	3] 0.03 4] 0.01
		Blessed Information Memory	1] 17.1 (4.4) 2] 18.4 (4.8)	3] 0.10			1] 14.5 (6.7) 2] 16.8 (7.7)	3] 0.07 4] 0.33
		RPM	1] 5.6 (3.9) 2] 6.7 (4.8)	3] 0.32			1] 6.3 (4.7) 2] 3.8 (3.7)	3] 0.01 4] 0.03
		Supra-Span Verbal Learning	1] 2.1 (2.2) 2] 2.4 (2.7)	3] 0.76			1] 2.7 (3.4) 2] 1.5 (2.3)	3] 0.12 4] 0.24
		Block Tapping Task	1] 3.3 (4.0) 2] 3.7 (2.7)	3] 0.04			1] 2.8 (3.4) 2] 4.0 (3.8)	3] 0.03 4] 0.47
		Token Test	1] 21.9 (6.9) 2] 24.5 (7.1)	3] 0.04			1] 17.4 (9.9) 2] 21.8 (9.5)	3] 0.02 4] 0.41
		SBI*	1] 33.2 (8.5) 2] 29.7 (9.5)	3] 0.03			1] 41.7 (13.7) 2] 35.8 (13.6)	3] 0.02 4] 0.12

EvTable6. Study results: Carnitine (ALCAR).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline				**FINAL 12m**	
Thal, 2000a	MITT Analysis 1] Placebo 2] ALCAR 1g tid 3] Difference between ALCAR and placebo in change from baseline	<u>ADAS-cog</u> <u>CDR</u> ADAS-Non cog MMSE ADL	1] 22.9 (1.1) 2] 23.1 (1.2) 1] 5.1 (0.2) 2] 5.3 (0.3) 1] 3.2 (0.3) 2] 3.3 (0.3) 1] 20.6 (0.4) 2] 20.1 (0.5) 1] 7.1 (0.2) 2] 7.1 (0.2)				1] 30.4 (1.6) 2] 30.0 (1.7) 1] 6.8 (0.4) 2] 7.1 (0.4) 1] 5.3 (0.6) 2] 5.2 (0.5) 1] 17.3 (0.7) 2] 17.5 (0.8) 1] 8.3 (0.3) 2] 8.6 (0.4)	3] 0.58 3] 0.69 3] 0.89 3] 0.10 3] 0.43

→ Modified ITT sample

EvTable7. Study results: Carnitine (ALCAR).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12m**	
Thal, 1996a Brooks, 1998	ITT Population 1] Placebo 2] ALCAR 3g/d 3] ALCAR vs. Placebo 4] Placebo < 65 years 5] Placebo < 65 years 6] ALCAR < 65 years 7] ALCAR > 65 years 8] Difference between Placebo and ALCAR change from baseline for subgroup <65yrs 9] Difference between Placebo and ALCAR change from baseline for subgroup >65yrs.	<u>ADAS-cog</u> <u>CDR</u> MMSE ADAS-non cog ADL IADL CGI-S CGI-C	1] 26.0 (10.5) 2] 25.4 (9.8) 4] 25.8 (10.5) 5] 26.0 (10.5) 6] 27.8 (10.5) 7] 24.9 (9.5) 1] 6.6 (2.7) 2] 6.3 (2.4) 4] 6.2 (2.6) 5] 6.7 (2.7) 6] 6.1 (2.3) 7] 6.4 (2.4) 1] 9.6 (3.9) 2] 19.8 (3.9) 1] 4.7 (4.2) 2] 4.4 (3.8) 1] 7.6 (2.1) 2] 7.4 (2.1) 1] 16.8 (6.0) 2] 16.8 (5.7) 1] 3.6 (0.7) 2] 3.5 (0.6)				1] 33.0 (14.3) 2] 32.8 (14.8) 4] 35.1 (14.2) 5] 32.4 (14.4) 6] 34.7 (16.2) 7] 32.3 (14.5) 1] 8.8 (3.7) 2] 8.7 (3.8) 4] 9.5 (4.3) 5] 8.0 (3.7) 6] 8.5 (3.4) 7] 8.9 (3.8) 1] 15.8 (6.2) 2] 16.5 (6.4) 1] 7.6 (6.3) 2] 7.0 (6.3) 1] 10.1 (4.1) 2] 9.9 (4.2) 1] 20.3 (6.6) 2] 20.8 (6.0) 1] 4.1 (0.9) 2] 3.9 (0.9) 1] 4.8 (0.9) 2] 4.9 (0.9)	3] 0.434 8] 0.11 9] 0.085 3] 0.562 8] 0.056 9] 0.047 3] 0.818 3] 0.466 3] 0.733 3] 0.62 3] 0.172 3] 0.358

EvTable8. Adverse Events: Carnitine (ALCAR).

Adverse events (AE) identified in included studies	Livingston, 1991	Rai, 1989	Sano, 1992	Spagnoli, 1991	Thal, 1996a	Thal, 2000a
Withdrawn (%) due to AE	T: 0 C: 0	T: 44 C:22	T: 0 C: 0	T: 0 C: 0	T: 3 C: 1	T: 1 C: 3
AE Checklist (Max 5)	3	3	3	3	1	1
None Reported						
Balance						
Accidental Injury						
Dizziness		X				
Falls						
Behavioral		X				
Agitation		X		NS		
Cardiovascular						
Arrhythmia						
Hypotension						
Hypertension						
Extrapyramidal						NS
Tremor						
Gastrointestinal	X					NS
Abdominal pain			X			
Constipation						
Diarrhea	X					
Dyspepsia						
Nausea, vomiting	X	X	X			
Metabolic/nutritional					NS	
Eating disorder						
Weight Change						
Neurological						
Asthenia						
Psychiatric		X				
Anxiety						
Confusion, delirium		X				
Depression		X				
Respiratory						NS
Cough, cold, infection						
Rhinitis						
Other					S	
Aberrant hematology						
Fatigue, weakness						
Fever, flu, pneumonia						
Headache						
Hepatic abnormality						
Muscle/joint disorder						
Pain						
Rash, skin disorder	X				NS	
Sleep disorder						
Urinary disorder						NS

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable9. Key characteristics: Donepezil (DPZ).

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Burns 1999	IF	6	Placebo Donepezil	DSM-III-R NINCDS	PDD	Mild-Mod	818	631	72y (50-93y) 42%M 99% white	5 mg/d for 7 d, then 10 mg/d	24w + 6w placebo washout period	ADAS-Cog CDR-SB CIBIC+ IDDD QOL	No
Feldman 2001 Auxiliary: Gauthier 2002	IF	8	Placebo Donepezil	NINCDS	AD	Moderate-Severe	290	247	73.7y (51-92y) 39%M Community	10 mg/d	24w	CAUST CIBIC CIBIC+ CSS DAD FRS IADL+ sMMSE NPI PSMS+ SF 36 SIB	MMSE Psychoactive drug use
Mohs 2001	IF	5	Placebo Donepezil	NINCDS DSM IV	AD	Probable	431	111	75.4y (50-93y) 37%M 92.15% white 2.75% black 5.1% other	10 mg/d	54w	ADL ADFACS CDR IADL IDDD MMSE	No

EvTable9. Key characteristics: Donepezil (DPZ) cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Prasher 2002	IF	6	Placebo Donepezil (DPZ)	ICD-10	AD	Mild–Mod	30	27	54y (43-66y) 50%M Community (99%) Institution (1%)	10 mg/d	24w	ABS DMR NPI SIB	Down Syndrome only
Pratt 2002	IF	5	Placebo Donepezil	NINCDS AIREN	VaD	Possible or Probable	893	707	74.0 (0.3)y range 41-95 Community	5 mg/d for 4w then either 5 or 10 mg/d for 20w	24w	ADAS-Cog CIBIC+ MMSE	No
Rogers 1996 Auxiliary: Rogers 2000 Neumann 1999 Rogers 1998	IF	6	Placebo Donepezil	DSM-III-R NINCDS	AD	Mild-Modly Sev	161	141	71.8y (54-85y) 40%M 99% white	5 mg/d	12w + 2w placebo washout period	ADAS-Cog ADL CDR-SB CGIC MMSE QoL	No
Rogers 1998a Auxiliary: Doody 2001 Steele 1999	IF	6	Placebo Donepezil	NINCDS DSM-III-R	AD	Mild-Modly severe	468	412	73.7y (50-94y) 36%M 96% white	5 mg/d for 7 d then 10 mg/d	15w	ADAS-Cog CIBIC+ MMSE CDR-SB QoL	No

EvTable9. Key characteristics: Donepezil (DPZ) cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Rogers 1998b Auxiliary: Doody 2001 Sparano 1998	IF	6	Placebo Donepezil	NINCDS DSM-III-R	AD	Mild-Mod	473	367	73.6 (51-94y) 38%M 95% white	10 mg/d	24w	ADAS-Cog CDR-SB CIBIC+ MMSE QoL	No
Tariot 2001a	IF	8	Placebo Donepezil	NINCDS	AD with CVD	Moderate-Severe	208	162	85.7y (65-100y) 18%M Institution (100%)	5 mg bid	24w	CDR-SB MMSE NPI-NH PSMS	MMSE Age

EvTable9. Key characteristics: Donepezil (DPZ) cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Thomas 2001	NR	7	Donepezil Vitamin E Rivastigmine (open label)	NINCDS	AD	Mild-Mod	60	54	66.5y (58-73y) 46%M	DPZ: 5 mg/d (month 1) 10 mg/d (until end) Vit E: 2000 IU (fixed) Rivastigmine: 1.5 mg/d (month 1) 3 mg/d (month 2) 6 mg/d (month 3) 9 mg/d (month 4) 12 mg/d (until end)	6m	ADAS-cog CT/MRI ERP scalp topography GBS GDS MMSE NPI WAIS	No
Winblad 2001b	IF	7	Placebo Donepezil	DSM IV NINCDS	AD	Mild–Mod	286	192	72.5y (50-87y) 36%M 100% white	10 mg/d	1y	ADL-PDS GBS GDS MMSE NPI PDS	APOE Genotype Gender

EvTable10. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12 w**		**Final: (specify) 24 w**	
Burns 1999	ITT analysis 1] Placebo 2] DPZ 5 mg/d 3] DPZ 10 mg/d 4] Placebo change from baseline 5] DPZ 5 change from baseline 6] DPZ 10 change from baseline 7] DPZ 5 vs. placebo 8] DPZ 10 vs. placebo 9] DPZ both doses vs. placebo	**ADAS-cog** **CIBIC+** CDR-SB IDDD QoL	1] 69.84(1.68)* 2] 67.78 (1.61) 3] 69.85 (1.71)		4] 0.45 5] -1.5 6] -1.8 4] 4.25 5] 4.05 6] 3.9 4] 0.15 5] -0.15 6] -0.18 4] 69.5 5] 69.0 6] 68.0	7] <0.0001 8] <0.0001 7] 0.0545 8] 0.0001 7] 0.0021 8] 0.0014 8] 0.0085	4] 1.5 5] 0.5 6] -1.4 4] 4.45 5] 4.25 6] 4.1 4] 0.375 5] 0.075 6] -0.13 4] 71.0 5] 70.8 6] 69.0	7] 0.0315 8] <0.0001 7] 0.0326 8] 0.0009 7] 0.0387 9] <0.05 8] 0.0020 8] 0.0163 4] NS 5] NS 6] NS

*SEM

EvTable11. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12 w**		**Final: (specify) 24w LOCF**	
Feldman 2001 Gauthier 2002	ITT Analysis 1] Placebo mean change from baseline 2] DPZ 10 mg/d mean change from baseline 3] Mean treatment difference DPZ vs. Placebo 4] Mean treatment difference LOCF population 5] Placebo change from baseline subgroup with MMSE of 10-17 6] DPZ 10 mg d change from baseline subgroup with MMSE of 10-17 7] Difference between Placebo and DPZ change from baseline subgroup with MMSE of 10-17	CIBIC+ CIBIC+ % improved DAD sMMSE SIB IADL + PSMS + NPI FRS			1] 4.1 2] 3.6 5] –0.11 6] –0.48 1] -305 2] 1.25 5] -4 6] 2 1] 0.2 2] 1.75 5] 0.0 6] 2.0 1] -0.25 2] 4.75 5] –1.0 6] 3.5 5] -0.5 6] –3.8	3] <0.0001 7] 0.0002 3] 0.0037 7] 0.0037 3] 0.0004 7] 0.0004 3] <0.0001 7] 0.0004	1] 4.65 2] 4.05 5] 0.24 6] –0.22 1] 42% 2] 63% 1] –8.98 2] -0.74 5] -9 6] 0.1 1] -0.5 2] 1.25 5] –0.5 6] 1.5 1] –4.0 2] 2.0 5] –3.0 6] 2.5 3] 6.83 3] 1.32 1] –1.0 2] 4.6 5]1.0 6] 5.0 1] -1.66 2] -0.38	3] 0.0004 7] 0.0044 3] <0.0001 3] <0.0001 7] <0.0001 3] 0.0019 7] 0.0009 3] <0.0001 7] 0.0012 3] 0.0015 3] 0.0015 7] 0.021 3] 0.0002 7] 0.0022

EvTable12. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 24 w**		**Final: (specify) 54 w**	
Mohs 2001	ITT Endpoint Analysis 1] Placebo 2] DPZ 10 mg d 3] Placebo mean change from baseline 4] DPZ mean 10mg/d change from baseline 5] Mean change from baseline DPZ vs. Placebo	ADFACS ADFACS ADL – Instrumental ADFACS ADL-basic MMSE Time to functional decline (days)	1] 17.1 (0.2)* 2] 17.1 (0.2)*		3] 0.4 4] 1.8	5] <0.01	3] 4.0 4] 2.5 3] –0.7 4] 0.6 3] 208 CI (165 to 252) 4] 356 CI (>280)	5] <0.001 5] 0.001 5] 0.007 5] <0.001 5] 0.0051

*SEM

EvTable 13. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 24 w**	
Prasher 2002	OC Analysis 1] Placebo 2] DPZ 10 mg d 5] Change from baseline placebo vs. DPZ 3] Placebo change from baseline 4] DPZ change from baseline 5] Change from baseline placebo vs. DPZ	<u>DMR</u> SIB NPI ABS	1] 58.2 (16.9) 2] 54.3 (16.1) 1] 27.2 (13.6) 2] 36.8 (21.9) 1] 8.0 (7.6) 2] 7.9 (5.8) 1] 93.0 (19.2) 2] 121.4 (36.9)				1] 64.4 (14.2) 2] 55.1 (17.9) 1] 11.2 (8.7) 2] 31.6 (28.2) 1] 3.6 (5.0) 2] 5.7 (7.6) 1] 84.5 (22.4) 2] 120.5 (44.1)	5] 0.22 3] 0.002 4] 0.002 5] 0.06 3] 0.03 3] 0.51

EvTable14. Study results: Denepezil.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 24 w	
Pratt 2002	ITT Analysis 1] Placebo change from baseline 2] Donepezil 5mg/d change from baseline 3] Donepezil 10mg/d change from baseline 4] Donepezil 5mg/d vs Placebo 5] Donepezil 10mg/d vs Placebo	<u>ADAS-cog</u> <u>CIBIC+</u> MMSE					1] 0.1 2] –1.1 3] –2.2 1] 32% 2] 46% 3] 36% 1] 0.5 2] 1.5 3] 1.6	4] <0.001 5] <0.001 4] 0.0006 5] 0.2096 4] <0.001 5] <0.001

EvTable15. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6w**		**Final: (specify) 12 w**	
Rogers 1996 Rogers 2000 Newman 1999 Rogers 1998	ITT Endpoint analysis 1] Placebo mean change from baseline 2] DPZ 1mg/d mean change from baseline 3] DPZ 3mg/d mean change from baseline 4] DPZ 5 mg/d mean change from baseline 5] Dose response analysis 6] DPZ 1 mg/d difference from placebo 7] DPZ 3 mg/d difference from placebo 8] DPZ 5mg/d difference from placebo	ADAS-Cog CGIC % success ADL MMSE QoL-P QoL-C CDR-SB			1] 0.5 2] -2.0 3] -3.2 4] -3.8 1] 0.8 2] 1.15 3] 1.25 4] 1.85 1] 0.10 2] -0.050 3] 0.0 4] -0.04		1] 0.7 2] -0.9 3] -1.4 4] -2.5 1] 80% 2] 82% 3] 83% 4] 90% 1] 1.5 2] 4.0 3] 0.6 4] -3.1 4] 1.2 2] 0.6 3] 0.9 4] 2.0 1] -1.3 2] 0.7 3] 2.6 4] 8.8 1] 3.7 2] -5.3 3] 0.0 4] 0.3 1] 0.10 2] 0.18 3] 0.23 4] -0.11	5] 0.0359 6] 0.105 7] 0.036 8] 0.002 8] 0.039 5] 0.0684 5] 0.0275 5] 0.0369 5] 0.8860 5] 0.3375

EvTable16. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6 w**		**Final: (specify) 12 w**	
Rogers 1998a Doody 2001 Steele 1999	ITT Analysis Endpoint 1] Placebo change from baseline 2] DPZ 5mg/d change from baseline 3] DPZ 10mg/dchange from baseline 4] DPZ 5mg/d vs placebo 5] DPZ 10mg/d vs placebo	ADAS-cog CIBIC + MMSE CDR-SB QoL			1] -0.02 2] -1.5 3] -2.9 1] 3.99 2] 3.85 3] 3.93 1] 0.65 2] 0.95 3] 1.4 1] -0.15 2] 0.0 3] -0.25	4] 0 .011 5] <0.001 5] 0.03 5] 0.008	1] 0.4 (0.43)* 2] -2.1 (0.43)* 3] -2.7 (0.43)* 1] 4.2 (0.07)* 2] 3.9 (0.08)* 3] 3.8 (0.08)* 1] 0.04 (0.25)* 2] 1.0 (0.25)* 3] 1.3 (0.24)* 1] -0.14 (0.11)* 2] -0.10 (0.11)* 3] -0.31 (0.11)* 1] 4.0 (2.7)* 2] 5.7 (2.7)* 3] -4.3 (2.7)*	4] <0.001 5] <0.001 4] 0.003 5] 0.008 4] <0.004 5] <0.001 4] 0.32 4] 0.65 5] 0.02

*SEM

EvTable17. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12 w**		**Final: (specify) 24 w**	
Rogers 1998b Doody 2001 Sparano 1998	ITT Population 1] Placebo 2] DPZ 5 mg/d 3] DPZ 10 mg/d 4] Placebo change from baseline 5] DPZSP5 change from baseline 6] DPZ10 change from baseline 7] DPZ5 vs placebo 8] DPZ10 vs. Placebo	<u>ADAS-cog</u> <u>CIBIC +</u> MMSE CDR-SB QoL			4] 1.25 5] -1.25 6] 2.0 4] 4.2 5] 3.95 6] 3.9 4] -0.5 5] 0.75 6] 1.0 4] 0.1 5] -0.2 6] -0.025	7] 0.0007 8] <0.0001 7] 0.0157 8] 0.009 7] 0.0002 8] <0.0001	4] 1.82 (0.49)* 5] -0.67 (0.51)* 6] -1.06 (0.51)* 4] 4.51 (0.08)* 5] 4.15 (0.09)* 6] 4.07 (0.07)* 4] -0.97 (0.28)* 5] 0.24 (0.29)* 6] 0.39 (0.29)* 4] 0.58 (0.14)* 5] -0.01 (0.14)* 6] -0.02 (0.14)*	7] <0.0001 8] <0.0001 7] <0.0047 8] <0.0001 7] 0.0007 8] 0.0002 7] 0.0008 8] 0.0007 7] NS 8] NS

*SEM

EvTable18. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12 w**		**Final: (specify) 24 w**	
Tariot 2001a	ITT Analysis 1] Placebo 2] DPZ 10 mg /d 3] Placebo change from baseline all patients 4] DPZ change from baseline all patients 5] Placebo change from baseline for subgroup with baseline MMSE scores of 10-26 6] DPZ change from baseline for subgroup with baseline MMSE scores of 10-26 7] mean change DPZ over Placebo 8] subjects >85 DPZ over Placebo	<u>NPI-NH</u> MMSE CDR-SB PSMS	1] 20.5 (14.7) 2] 21.0 (14.5) 1] 14.4 (5.8) 2] 14.4 (5.4) 1] 10.8 (3.7) 2] 11.2 (4.0) 1] 14.7 (5.0) 2] 15.1 (4.9)		3] -0.5 4] 0.35 5] -0.95 6] 0.6 3] 0.2 4] -0.15 5] 0.8 6] -0.3	6] <0.05 7] NS 4] 0.09 8] <0.05 7] 0.09	3] -4.9 (1.9)* 4] -2.3 (1.9)* 3] -0.75 4] -0.1 5] -1.0 6] 0.0 3] 0.7 4] -0.1 5] 0.8 6] -0.2 3] -1.0 4] -1.0	7] NS 7] NS 8] <0.05 4] <0.05 6] <0.05 7] <0.05 8] <0.05 7] 0.31

*SEM

EvTable19. Study results: Donepezil (DPZ), Vitamin E.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3 m**		**Final: (specify) 6 m**	
Thomas 2001	OC Analysis 1] DPZ 10 mg d 2] Vitamin E 2,000 IU 3] change from baseline with DPZ 4] change from baseline with Vitamin E 5] DPZ vs Vitamin E change from baseline	WAIS	1] 72 (2.0)* 2] 72 (2.0)*		1] 74 (2.0)* 2] 72 (2.0)*		1] 75 (2.0)* 2] 71 (2.1)*	3] 0.15 4] 0.43
		MMSE	1] 16 (0.5)* 2] 16 (0.5)*		1] 16 (0.6)* 2] 15 (0.5)*	5] <0.001 favors DZP	1] 16 (0.5)* 2] 15 (0.6)*	3] 0.06 4] 0.07 5] <0.001 favors DPZ
		ADAS-cog	1] 33.34 (2.7)* 2] 33.45 (2.6)*		1] 31.55 (2.7)* 2] 36.09 (2.8)*		1] 31.84 2.7)* 2] 39.07 (2.7)*	3] <0.001 4] <0.01
		NPI	1] 21.9 (0.5)* 2] 21.9 (0.5)*				1] 16.8 (0.2)* 2] 22.8 (1.2)*	

*SEM

EvTable20. Study results: Donepezil (DPZ).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 24 w**		**Final: (specify) 52 w**	
Winblad 2001b	ITT Endpoint Analysis 1] Placebo 2] DPZ 10 mg/d 3] Placebo change from baseline 4] DPZ change from baseline 5] DPZ vs. Placebo 6] Analysis for APOE Genotype Interaction 7] Aanlysis for Gender Interaction	<u>GBS total score</u> GBS MMSE ADL-PDS GDS NPI				5] NS	3] 12.0 4] 9.0 3] -2.2 4] -0.4 3] -15 4] -11	5] 0.054 6] 0.532 7] 0.258 5] 0.012 5] <0.001 6] 0.712 7] 0.743 5] <0.05 5] 0.047 5] NS

EvTable21. Adverse Events: Donepezil (DPZ).

Adverse events (AE) identified in included studies	Burns, 1999	Feldman, 2001	Mohs, 2001	Prasher, 2002	Pratt, 2002	Rogers, 1996	Rogers, 1998a	Rogers, 1998b	Tariot, 2001a	Thomas, 2001	Winblad, 2001b
Withdrawn (%) due to AE	T:14+ C:10	T: 8 C: 6	T: 11 C: 7	T: 7 C: 0	T:15+ C: 9	T: 8 C: 5	T: 7+ C: 1	T:11+ C: 7	T: 18 C: 11	T: 0 C: 0	T: 7 C: 6
AE Checklist (Max 5)	3	2	3	4	1	2	3	3	2	3	4
None Reported										X	
Balance											S
Accidental Injury		X	NS			X	NS*		X		NS
Dizziness	NS*	X		NS		X	NS*	NS*	X		NS
Falls											
Behavioral		X									NS
Agitation			NS	NS		X	NS*		X		
Cardiovascular									X		
Arrhythmia							X				
Hypotension											
Hypertension											
Extrapyramidal											
Tremor									X		
Gastrointestinal						X	X				
Abdominal pain		X		NS			X		X		NS
Constipation						X					NS
Diarrhea	S*	X	S	NS		X	S*	S*	X		NS
Dyspepsia			S								
Nausea, vomiting	S*	X	S	NS		X	S*	S*	X		NS
Metabolic/nutritional									X		
Eating disorder	NS*		S	NS			X	NS*	X		
Weight Change		X	NS				X		X		
Neurological				NS							
Asthenia		X	NS						X		S
Psychiatric				X							
Anxiety											NS
Confusion, delirium	NS*	X							X		NS
Depression		X									NS
Respiratory		X				X	X				
Cough, cold, infection						X	NS*		X		
Rhinitis			NS				X	NS*	X		
Other						X	X		X		
Aberrant hematology								NS*	X		
Fatigue, weakness				S			NS*	S*			
Fever, flu, pneumonia									X		X
Headache		X	S			X	NS*		X		NS
Hepatic abnormality	NS*					NS	NS				
Muscle/joint disorder		X		NS			NS*	S*	X		
Pain		X				X	NS*		X		
Rash, skin disorder			NS						X		
Sleep disorder	NS*		NS	NS			S*				NS
Urinary disorder		X	S			X	S		X		NS

NR = Withdrawals due to AE Not Reported; + = Dose effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable22. Key characteristics: Galantamine.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Erkinjuntti 2002	PI	8	Placebo Galantamine	NINDS NINCDS	VaD AD	Probable	592	457	75.1y (40-90y) 53%M 99.9% white	4 mg/d on w 1 8 mg/d on w 2 12 mg/d on w 3 16 mg/d on w 4 20 mg/d on w 5 24 mg/d from w 6 to the end	6m	ADAS-Cog CIBIC+ DAD NPI	MID vs AD+vascular
Raskind 2000	IF	8	Placebo Galantamine	NINCDS	AD	Mild-Mod	636	438	75.4y (NR) 38%M 91.5% white	Loading: 8 mg/d on w 1 16 mg/d on w 2 24 mg/d on w 3 Then one group stayed at 24 mg/d the other group 32 mg/d	6m	ADAS-Cog CIBIC+ DAD	APOE Genotype
Rockwood 2001	IF	7	Placebo Galantamine	NINCDS	AD	Probable Mild-Mod	386	288	74.9y (NR) 44%M	8 mg/d on w 1 16 mg/d in w 2 24 mg/d on w 3 32 mg/d on w 4 At the end of w 4 dose could be reduced to 24 mg/d	3m	ADAS-Cog CIBIC+ DAD NPI PSQI	No
Tariot 2000	NR	8	Placebo Galantamine	NINCDS	AD	Probable Mild-Mof	978	679	76.8y (NR) 36%M 93% white	Loading: 8 mg/d 16 mg/d Then 24 mg/d	5m	ADAS-Cog ADCS CIBIC+ IADL NPI	No

EvTable22. Key characteristics: Galantamine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Wilcock 2000 Auxiliary: Wilcock 2001	NI	8	Placebo Galantamine	NINCDS	AD	Mild-Mod	653	525	72.2y (NR) 37%M	Loading: 8 mg/d on w 1 16 mg/d on w 2 24 mg/d on w 3 one group stayed at 24 mg/d the other group 32 mg/d	6m	ADAS-Cog ADAS CIBIC+ DAD	MMSE APOE Genotype
Wilkinson 2001	IF	7	Placebo Galantamine	NINCDS DSM-III-R	AD	Mild–Mod	285	206	73.8y (>45y) 42%M 100% Community	Start at 4 mg/d and progressively increased every 2-3 d to reach the target doses 18mg/d 24 mg/d 36 mg/d	12w	ADAS-Cog CGIC PDS	No

EvTable23. Study results: Galantamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6m	
Erkinjuntti 2002	OC Analysis 1] Placebo from baseline 2] Galantamine 24 mg/d from baseline 3]Placebo vs Galantamine 4] Placebo from baseline subgroup AD+vascular 5] Galantamine from baseline subgroup AD+vascular 6] Placebo vs Galantamine subgroup AD+vascular 7] Placebo from baseline subgroup VAD 8] Galantamine from baseline subgroup VAD 9] Placebo vs Galantamine subgroupVAD	<u>ADAS-cog/11 change from baseline</u> <u>CIBIC-plus % improved or stable</u> CIBIC-plus % improved ADAS-cog/13 Change from baseline DAD NPI					1] 1.0 (0.5)* 2] –1.7 (0.4)* 4] 1.8 (0.6)* 5]-1.0 (0.46)* 7] –0.4 (0.78)* 8] –2.4 (0.59)* 1] 59% 2] 74% 4] 54% 5] 75% 4] 19% 5] 32% 7] 23% 8] 31% 1] 0.9 (0.6)* 2] –2.4 (0.4)* 1] –4.4 (1.3)* 2] 0.2 0.9)* 1] 1.0 (0.9)* 2] –1.2 0.6)*	1] 0.045 2]<0.0001 3]<0.0001 6] 0.0005 9] 0.06 3] 0.0011 6] 0.001 6] 0.019 9] 0.238 3]<0.0001 3] 0.0017 3] 0.0164

*SEM

EvTable24. Study results: Galantamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6m	
Raskind 2000	ITT Analysis 1] Placebo change from baseline 2] Galantamine 24 mg/d change from baseline 3] Galantamine 32 mg/d change from baseline 4] Placebo vs. Galantamine 24mg/d change from baseline 5] Placebo vs. Galantamine 32 mg/d change from baseline	<u>ADAS-cog/11</u> <u>CIBIC-plus</u> <u>% improved</u> DAD (total)					1] 2.0 (0.45)* 2] 1.9 (0.36)* 3] –1.4 (0.44)* 1] 13.8% 2] 19.9% 3] 15.8%	4] <0.001 5] <0.001 4] <0.05 5] <0.05 4] NS 5] NS

*SEM

EvTable25. Study results: Galantamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 3m	
Rockwood 2001	ITT Analysis 1] Placebo change from baseline 2] Galantamine 24-32mg/d change from baseline 3] Difference between placebo and galantamine change from baseline	ADAS-Cog-11 ADAS-Cog-13 CIBIC-+ % improved or stable NPI DAD					1] 0.6 (0.45)* 2] –1.1 (0.33)* 1] +0.7 (0.51)* 2] –1.2 (0.38)* 1] 18.7% 2] 22.1% 1] 0.5 (0.65)* 2] –0.3 (0.7)* 1] –5.2 (1.18)* 1] –0.4 (0.76)	3] <0.01 3] <0.01 3]<0.01 1] NS 2] NS 3]<0.001

*SEM

EvTable26. Study results: Galantamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 5m	
Tariot 2000	ITT Analysis 1] Placebo change from baseline 2] Galantamine 8mg/d change from baseline 3] Galantamine 16 mg/d change from baseline 4] Galantamine 24mg/d change from baseline 5] Placebo vs. galantamine 8 mg/d in change from baseline 6] Placebo vs. galantamine 16 mg/d in change from baseline 7] Placebo vs. galantamine 24 mg/d in change from baseline 8] Galantamine 8mg/d vs. 16mg/d in change from baseline 9] Galantamine 8mg/d vs. 24mg/d in change from baseline	ADAS-Cog CIBIC+ % improved ADCS/ADL NPI					1] 1.7 (0.39)* 2] +0.4 (0.52)* 3] –1.4 (0.35)* 4] –1.4 (0.39)* 1] 49% 2] 53% 3] 66% 4] 64% 1] –3.8 (0.6)* 2] –3.2 (0.8)* 3] –0.7 (0.5)* 4] –1.5 (0.6)* 1] 2.0 (0.7)* 2] 2.3 (1.0)* 3] –0.1 (0.7)* 4] 0.0 (0.8)*	5] NS 6]<0.001 7]<0.001 8] <0.05 9] <0.01 6] <0.001 7] <0.001 8] <0.05 9] <0.05 6]<0.001 7] <0.01 8] <0.01 6] <0.05 7] <0.05

*SEM

EvTable27. Study results: Galantamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6m	
Wilcock 2000 Wilcock 2001	ITT Analysis 1] Placebo change from baseline 2] Galantamine 24mg/d change from baseline 3] Galantamine 32 mg/d change from baseline 4] Difference between placebo and Galantamine 24mg/d in change from baseline 5] Difference between placebo and Galantamine 32 mg/d in change from baseline	<u>ADAS-cog</u> <u>DAD</u> <u>CIBIC+</u>					1] 2.4 (0.41)* 2] –0.5 (0.38)* 3] –0.8 (0.43)* 1] –6.0 (1.08)* 2] –3.2 (1.02)* 3] -2.5 (1.07)* 1] 16.5% 2] 17% 3] 25%	1] <0.001 2] <0.001 3] <0.001 4] <0.001 5] <0.001 4] 0.1 5] <0.05 4] <0.05 5] <0.001

*SEM

EvTable28. Study results: Galantamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
Wilkinson 2001	ITT Analysis 1] Placebo change from baseline 2] Galantamine 18 mg/d Change from baseline 3] Galantamine 24 mg/d Change from baseline 4] Galantamine 36 mg/d Change from baseline 5] Placebo vs. Galantamine 18mg/d in change from baseline 6] Placebo vs. galantamine 24mg/d in change from baseline 7] Placebo vs. galantamine 36mg/d in change from baseline	<u>ADAS-Cog</u> CGIC % improved PDS-1 % improved					1] 1.6 (0.7)* 2] –01 (0.7)* 3] –1.4 (0.9)* 4] –0.7 (0.7)* 1] 31.3% 2] 36.7% 3] 28.3% 4] 31.9% 1] 9.2 % 2] 12.5 % 3] 14.3% 4] 7.4%	5] NS 6] <0.01 7] 0.08 5] NS 6] NS 7] NS 5] NS 6] NS 7] NS

*SEM

EvTable29. Adverse Events: Galantamine.

Adverse events (AE) identified in included studies	Erkinjuntti, 2002	Raskind, 2000	Rockwood, 2001	Tariot, 2000	Wilcock, 2000	Wilkinson, 2001
Withdrawn (%) due to AE	T: 20 C: 8	T: 27 C: 8	T: 26 C: 4	T: 8 C: 7	T: 18 C: 9	T: 27+ C: 9
AE Checklist (Max 5)	3	3	4	3	3	3
None Reported						
Balance						
Accidental Injury	X					
Dizziness		X	X		X	X
Falls						
Behavioral						
Agitation			X	X		
Cardiovascular						
Arrhythmia						
Hypotension						
Hypertension						
Extrapyramidal						
Tremor		X				
Gastrointestinal	X			X		
Abdominal pain		X	X			
Constipation						
Diarrhea		X		X	X	X
Dyspepsia						
Nausea, vomiting	X	X	X	X	X	X
Metabolic/nutritional						
Eating disorder		X	X	X	X	X
Weight Change		S		X	S	
Neurological	X					
Asthenia						
Psychiatric						
Anxiety						
Confusion, delirium						
Depression						
Respiratory						
Cough, cold, infection						
Rhinitis						
Other						
Aberrant hematology		NS	NS	NS	NS	NS
Fatigue, weakness						
Fever, flu, pneumonia						
Headache					X	X
Hepatic abnormality						
Muscle/joint disorder				X		
Pain						
Rash, skin disorder						
Sleep disorder			X			
Urinary disorder						

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable30. Key characteristics. Metrifonate.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Becker 1996	NI	6	Placebo Metrifonate	NINCDS	AD	Probable	53	51	71.4y (57-85y) 40%M	Loading: 5.0 mg/kg for 2 w, 4.9 mg/kg for 1 w then 2.1 mg/kg weekly	3m	ADAS-Cog ADAS-Noncog ADAS-T ADLC Laboratory tests EEG GIS MMSE	No
Becker 1998	NI	6	Placebo Metrifonate	NINCDS	AD	Probable	47	46	73.0y (<90y) 51%M Community	Loading2 mg/kg for 5 d, 0.95 mg/kg on d 6 then 2.9 mg/kg weekly	6m	ADAS-Cog ADAS-Noncog ADLC Laboratory tests GIS MMSE	No

EvTable30. Key characteristics: Metrifonate cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Cummings 1997	NR	5	Placebo Metrifonate	NINCDS	AD	Probable Mild-Mod	480	453	NR	Loading: Low dose group: 0.5 mg/kg Medium-dose group: 0.9 mg/kg High-dose group: 2.0 mg/kg Maintenance dose respectively: 0.2 mg/kg 0.3 mg/kg 0.65 mg/kg/d	12w	ADAS-Cog CIBIC+ MMSE	No
Cummings 1998 AUXILIARY Cummings 1998b	PI	8	Placebo Metrifonate	NINCDS	AD	Probable	480	443	73.5y (NR) 41%M	Loading for 2 w: low dose group 0.5 mg/kg ; mid-dose group: 0.9 mg/kg; high-dose group 2.0 mg/kg then respectively 0.2 mg/kg 0.3 mg/kg 0.65 mg/kg	12w	ADAS-Cog CIBIC+ CIBIS+ GERRI IADL MMSE PSMS	No

EvTable30. Key characteristics: Metrifonate cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Dubois 1999 AUXILIARY McKeith 1998	IF	6	Placebo Metrifonate	DSM IV	AD	Mild-Mod	605	516	72.1y (NR) 36%M	1 loading dose of 80 mg or 120 mg and then: 0.65 mg/Kg/d or 1.0 mg/Kg/d	26w	AChE ADAS-Cog ADAS-Noncog CIBIC+ CIBIS+ DAD ECG GDS MMSE NPI Laboratory tests	No
Jann 1999	PI	6	Placebo Metrifonate	NINCDS	AD	Mild-Mod	395	393	75.0y (45-90y) 42%M 91% White 3.8% Black 2.6% Hispanic 1.8% Asian	Loading dose group: 100 or 150 mg for 2 w Non loading dose group: 50 mg/d	6w	ADAS-Cog ADAS-Noncog CIBIC+ CIBIS+ EEG MMSE	No

EvTable30. Key characteristics: Metrifonate cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	#Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Morris 1998	PI	7	Placebo Metrifonate	NINCDS	AD	Mild-Mod	408	334	73.6y (NR) 39%M 93% White 3.3% Black 0.4% Asian 2.6% Hispanic	2 w loading (2.0mg/kg/d) 24w 0.65 mg/kg/d	26w	ADAS-Cog ADAS-NONCOG CIBIC+ CIBIS+ GDS MMSE NPI	No
Pettigrew 1998	PI	6	Placebo Metrifonate	NINCDS	AD	Probable	27	27	72.0y (55-85y) 59%M 100% community	Loading for 6 d: Panel 1: 1.5 mg/kg Panel 2: 2.5 mg/kg Panel 3: 4 .0 mg/kg Panel 4: 4.0 then respectively: 0.25 mg/kg; 4.0 mg/kg; 0.65 mg/kg 1.0 mg/kg	21d	ADAS-Cog ADAS-Noncog Blessed – DRS ECG MMSE MRS	No

EvTable30. Key characteristics: Metrifonate cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Raskind 1999	IF	7	Placebo Metrifonate	NINCDS	AD	Probable Mild-Mod	264	219	74.6y (NR) 36% M Community 90% White 3.7% Black 5.1% Hispanic 0.3% American Indian	50 mg/d	6m + 6 w post-treatment follow-up period	ADAS-Cog ADAS-Noncog CIBIC+ CIBIS+ DAD GDS MMSE NPI	No

EvTable31. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 3 m**	
Becker 1996	OC Analysis 1] Placebo 2] Metrifonate 5.0 mg/kg 2 w 4.9 mg/kg 1 w 2.1 mg/kg 9w 3] Baseline vs. Placebo 4] Baseline vs. Metrifonate 5] Metrifonate vs. placebo	<u>ADAS-Cog</u> MMSE ADAS-Noncog ADAS-Total GIS ADLC	1] 26.39(10.20) 2] 25.64(11.86) 1] 19.30 (5.50) 2] 19.47 (5.35) 1] 5.19 (5.38) 2] 5.91 (4.93) 1] 31.58(13.29) 2] 31.56(14.56) 1] 3.63 (0.46) 2] 4.08 (0.52) 1] -2.51(13.26) 2] -7.80(17.21)				1] 27.49(11.04) 2] 24.89(11.80) 1] 18.35 (5.77) 2] 19.36 (6.01) 1] 5.88 (5.74) 2] 5.94 (5.11) 1] 33.37(14.51) 2] 30.83(14.44) 1] 4.11 (0.59) 2] 4.10 (0.71) 1] -2.23 (9.31) 2] -3.82(17.00)	3] <0.02 4] 0.15 5] <0.01 3] <0.03 4] 0.76 5] 0.14 3] 0.09 4] 0.88 5] 0.11 3] <0.02 4] 0.21 5] <0.01 3] <0.01 4] 0.90 5] 0.1 3] 0.93 4] 0.17 5] 0.80

EvTable32. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6m**	
Becker 1998	OC Analysis 1] Placebo 2] Metrifonate 2.9 mg/kg w 3] Placebo vs. baseline 4] Metrifonate vs. baseline 5] Metrifonate vs. Placebo	<u>ADAS-Cog</u> MMSE ADAS-Noncog GIS ADLC	1] 21.75 (8.40) 2] 20.61 (9.33) 1] 19.78 (4.92) 2] 20.62 (3.85) 1] 3.75 (4.53) 2] 2.72 (3.57) 1] 3.85 (0.77) 2] 3.78 (0.45) 1] 3.88 (8.66) 2] 4.93 (6.66)				1] 23.42 (9.53) 2] 20.61 (9.32) 1] 18.60 (5.40) 2] 20.38 (4.42) 1] 4.07 (4.92) 2] 2.80 (3.40) 1] 4.23 (0.81) 2] 4.34 (0.80) 1] 9.56 (10.93) 2] 8.94 (8.67)	3] 0.01 4] 1.00 5] <0.03 3] <0.01 4] 0.44 5] 0.09 3] 0.31 4] 0.80 5] 0.53 3] <0.02 4] <0.00 5] 0.42 3] 0.01 4] 0.00 5] 0.58

EvTable33. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12 w	
Cummings 1997	OC Population 1] Placebo 2] Low Dose Metrifonate 0.5 mg/kg loading 0.2 mg/kg maintenance 3] Medium Dose Metrifonate 0.9 mg/kg loading 0.3 mg/kg maintenance 4] High dose Metrifonate 2.0 mg/kg loading 0.65 mg/kg maintenance 5] Placebo vs. medium dose Metrifonate 6] Placebo vs. high dose Metrifonate	ADAS-Cog CIBIC+					5] 1.45 6] 3.17 5] 0.33 6] 0.40	5] <0.05 6] <0.001 5] <0.05 6] <0.001

EvTable34. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Cummings 1998a Cummings 1998b	ITT Analysis 1] Placebo 2] Metrifonate 20 mg qid difference from Placebo 3] Metrifonate 25mg qid difference from Placebo 4] Metrifonate 60mg qid difference from Placebo	<u>CIBIC+</u> <u>ADAS-Cog</u> MMSE PSMS CIBS+ GERRI IADL					2] 0.04 CI (-0.16-0.24) 3] 0.29 CI (0.09-0.48) 4] 0.35 CI (0.15-0.54) 2] 1.5 CI (0.18-2.83) 3] 1.30 CI (-0.02-2.62) 4] 2.94 CI (1.61-4.27) 2] 1.11 C1(0.39 - 1.84) 3] 0.63 C1(-0.10-1.35) 4] 1.37 C1(0.64 - 2.10)	2] 0.735 3] 0.005 4] 0.0007 2] 0.02 3] 0.053 4] 0.0001 2] 0.0029 3] 0.0905 4] 0.0003 2] NS 3] NS 4] NS 2] NS 3] NS 4] NS 2] NS 3] NS 4] NS 2] NS 3] NS 4] NS

EvTable35. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 26 w**	
Dubois 1999 McKeith 1998	ITT Analysis (LOCF) 1] Placebo 2] Metrifonate 40 to 50 mg/d variable by weight 3] Metrifonate 60 to 80 mg/d variable by weight 4] mean change from baseline Placebo vs. 40/50mg dose Metrifonate 5] mean change from baseline Placebo vs. 60/80 mg dose Metrifonate	ADAS-cog CIBIC+ DAD total MMSE CIBIS+ ADAS-Noncog Total NPI total GDS IADL ADL					3] 1.3 4] 3.24 3] 0.21 4] 0.35 3] 3.00 4] 5.45 3] 0.40 4] 1.19 3] 0.20 4] 0.23 3] 0.59 4] 1.37 3] 0.83 4] 1.44 3] 0.08 4] 0.21	3] 0.032 4] 0.0001 3] 0.052 4] 0.0014 3] 0.0522 4] 0.0005 3] 0.26 4] 0.0009 3] 0.0002 4] 0.0001 3] 0.14 4] 0.0008 3] 0.48 4] 0.23 3] 0.22 4] 0.0026 3] <0.05 4] <0.05 3] NS 4] NS

EvTable36. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 4w**		**Final: (specify) 6w**	
Jann 1999	ITT Analysis 1] Placebo 2] Metrifonate loading dose 100/150 mg d 2w by weight plus 50 mg d 4 w 3] Metrifonate 50 mg d 6w 4] Placebo change from baseline 5] Metifonate loading dose change from baseline 6] Metrifonate no loading dose change from baseline 7] Metrifonate loading dose vs. placebo change from baseline 8] Metrifonate no loading dose vs Placebo change from baseline	<u>ADAS-Cog</u> CIBIC+ ADAS-Noncog CIBIS+ MMSE			4] 0.0 5] -0.85 6] -0.1 4] 4.02 5] 4.25 6] 3.85	7] NS 7] <0.05	4] 0.55 5] -1.0 6] 0.0 4] 4.1 5] 3.9 6] 3.72	7] 0.01 8] NS 7] <0.05 8] <0.05 7] NS 8] NS 7] NS 8] NS 7] NS 8] NS

EvTable37. Study results: **Metrifonate.**

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12w**		**Final: (specify) 26w**	
Morris 1998	ITT Analysis 1] Placebo 2] Metrifonate 180mg loading 60mg maintenance 3] Difference between Placebo and Metrifonate change from baseline 4] Placebo change from baseline 5] Metrifonate change from baseline	ADAS-Cog CIBIC+ DAD GDS ADAS-Noncog MMSE			4] 1.5 5] –0.5 1] 4.15 2] 3.95	3] 0.0002 3] 0.0152	1] 2.7 2] -0.3 3] 2.86 CI (1.37-4.34) 4] 2.5 5] –0.3 1] 4.35 2] 4.05 3] 0.28 CI (0.06-0.50) 4] 4.38 5] 4.05	3] 0.0001 3] 0.0071 3] 0.0860 3] 0.0734 3] 0.1221 3] 0.1788

EvTable38. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 21d	
Pettigrew 1998	OC Analysis							
	1] Placebo change from baseline	ADAS-Cog					1] 0.00 (3.65) 2] 1.67 (2.52) 3] 1.33 (4.04) 4] –1.33 (2.4) 5] –2.63 (6.7)	
	2] Metrifonate 135mg loading 25mg maintenance change from baseline	ADAS-Noncog					1] –1.86 (2.1) 2] –3.67 (1.5) 3] 1.33 (5.77) 4] –2.00 (2.1) 5] –1.75 (2.6)	
	3] Metrifonate 225mg loading 35mg maintenance change from baseline	MMSE					1] 0.71 (2.50) 2] –0.67 (3.5) 3] 1.33 (0.58) 4] 0.50 (1.87) 5] 2.63 (2.07)	
	4] Metrifonate 335mg loading 60mg maintenance change from baseline	Blessed-DRS					1] –2.64 (2.46) 2] –1.17 (2.52) 3] 0.50 (2.29) 4] 0.67 (3.40) 5] 0.56 (1.66)	
	5] Metrifonate 335mg loading 90mg maintenance change from baseline							

EvTable39. Study results: Metrifonate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12 w**		**Final: (specify) 26 w**	
Raskind 1999	ITT analysis 1] Placebo 2] Metrifonate 50 mg d 3] Placebo mean change from baseline 4] Metrifonate mean change from baseline 5] Metrifinate vs. placebo 6] Mean drug-placebo difference change from baseline	MMSE NPI CIBIC+ GDS ADAS-Cog ADAS-Noncog DAD CIBIS+			3] -0.60 4] 0.75 3] 4.2 4] 4.05	5] <0.05	3] -1.25 4] 0.60 3] .075 4] 0.30 3] 4.4 4] 4.78	6] 0.0001 5] <.05 6] 0.013 5] <0.05 5] <0.05 6] 0.039 6] 0.570 6] 0.012 6] 0.185 6] 0.036 6] 0.260

EvTable40. Adverse Events: Metrifonate.

Adverse events (AE) identified in included studies	Becker, 1996	Becker, 1998	Cummings, 1997	Cummings, 1998	Dubois, 1999	Jann, 1999	Morris, 1998	Pettigrew, 1998	Raskind, 1999
Withdrawn (%) due to AE	T: 0 C: 0	T: 0 C: 0	T: 6 C: 4	T: 6 C: 4	T: 6 C: 6	T: 6 C: 2	T: 12 C: 4	T: 0 C: 0	T: 11 C: 9
AE Checklist (Max 5)	5	2	4	3	3	4	4	5	3
None Reported		X							
Balance					X				
Accidental Injury					X				
Dizziness	X				X			X	
Falls									
Behavioral									
Agitation	X							X	X
Cardiovascular	X		X						
Arrhythmia				X	X	X		X	
Hypotension					X			X	
Hypertension									
Extrapyramidal									
Tremor									
Gastrointestinal	X		X	X				X	
Abdominal pain	X		X	X				X	X
Constipation									
Diarrhea	X		X	X	X	S*	X	X	
Dyspepsia						X			
Nausea, vomiting	X		X	X	X	S*	X	X	
Metabolic/nutritional									
Eating disorder									
Weight Change									
Neurological								X	
Asthenia					X				
Psychiatric									
Anxiety									
Confusion, delirium									
Depression									
Respiratory	X								
Cough, cold, infection									
Rhinitis							X	X	X
Other	X		X	X	X			X	
Aberrant hematology					X				
Fatigue, weakness					X				
Fever, flu, pneumonia									
Headache	X								
Hepatic abnormality				X					
Muscle/joint disorder			X	X	X	S*	X		X
Pain									
Rash, skin disorder									
Sleep disorder	X							X	
Urinary disorder									

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable41. Key characteristics: Nicergoline.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Hermann 1997	NR	6	Placebo Nicergoline	DSM III	MID	Mild-Mod	139	136	73.5y (55-85y) 48%M	30 mg bid	6m	BL-A CGI DSPT DST DTIC HIS MMSE Laboratory Tests SCAG WAIS	No
Nappi 1997	IF	6	Placebo Nicergoline	DSM-III-R	PDD VaD Mixed	Mild-Mod	108	101	69.3y (55-81y) 55%M	30 mg bid	12m	CGI HAM-D MMSE Neurological Exam Physician Global Impression Patient Global Impression SCAG	No

EvTable41. Key characteristic:. Nicergoline cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Saletu 1995 AUXILIARY Saletu 1997	NR	6	Placebo Nicergoline	DSM-III-R	SDAT MID	Mild-Mod	112	98	Mean NR (>60y) %M NR	30 mg bid	8w	AAMD CGI CT Scan EEG/ERG Mapping Ham-D Laboratory tests MMS NOSIE SCAG TESS-DOTES	SDAT vs MID
Winblad 2001a	IF	6	Placebo Nicergoline	NINCDS DSM-III-R	AD	Probable Mild–Mod	346	285	73.7y (NR) 38%M	30 mg bid	6m	ADAS-cog ADAS-noncog ADAS-Total IADL CGIC CT/MRI ECG MMSE PSMS	No
DRUG VS DRUG													
Schneider 1994	NR	5	Nicergoline Antagonic Stress	DSM IV ICD-10	AD	Mild-Mod	62	NR	69.8y (65-85y) 53%M	60 mg/d	3m	SAS-G SCAG WAIS WMS	No

EvTable42. Study results: Nicergoline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 4m**		**Final: (specify) 6m**	
Hermann 1997	ITT Analysis 1] Placebo 2] Nicergoline 30 mg BID 3] change from baseline of differences between Placebo and Nicergoline	<u>SCAG</u>	1] 63.17(12.73) 2] 63.74(11.31)		1] 59.59(16.88) 2] 52.50(12.41)	3] <0.0001	1] 57.48(17.16) 2] 49.54(12.82)	3]<0.0001
		<u>MMSE</u>	1] 20.28 (2.62) 2] 20.23 (2.06)		1] 4.50 (1.07) 2] 3.69 (0.70)	3] <0.0001	1] 21.56 (3.81) 2] 24.03 (3.06)	3]<0.0001
		CGI (Item 2)	1] 5.02 (0.22) 2] 4.97 (0.18)		1] 22.31(10.19) 2] 24.17(10.21)	3] 0.1292	1] 4.43 (1.18) 2] 3.46 (0.92)	3]<0.0001
		WAIS-DST	1] 19.73 (8.73) 2] 20.62 (7.93)		1] 8.02 (1.57) 2] 8.93 (1.53)	3] .0004	1] 22.44 (9.91) 2] 5.37(11.08)	3] 0.0602
		WAIS-DSPT	1] .67 (1.63) 2] 7.56 (1.64)		1] 12.00 (4.78) 2] 13.66 (4.11)	3] 0.0328	1] 8.13 (1.66) 2] 8.98 (1.86)	3] 0.0042
		WAIS-DTIC	1] 10.63 (4.58) 2] 11.33 (4.08)		1] 10.41 (3.48) 2] 8.63 (3.54)	3] 0.0017	1] 12.15 (4.52) 2] 14.57 (3.79)	3] 0.0026
		Blessed-A scale	1] 10.85 (3.32) 2] 10.69 (3.35)				1] 9.94 (3.98) 2] 7.69 (3.75)	3] 0.0010

EvTable43. Study results: Nicergoline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6m**		**Final: (specify) 12m**	
Nappi 1997	OC Analysis 1] Placebo 2] Nicergoline 30 mg bid 3] Nicergoline difference from placebo	<u>SCAG</u> Total Score <u>MMSE</u> Physician Global Impression (% improved) Patient-Global Impression (% improved)	1] 49.14 (6.9) 2] 49.14 (9.2) 1] 21.98 (2.6) 2] 21.25 (2.9)		1] 50.12 (7.8) 2] 45.53 (10.4) 1] 20.35 (3.5) 2] 21.78 (4.0)	3] <0.05 3] <0.05	1] 53.72 (10.2) 2] 45.37 (11.7) 1] 19.14 (3.8) 2] 21.27 (4.1) 1] 10% 2] 53% 1] 8% 2] 64%	3] <0.001 3] <0.01 3] <0.001 3] <0.001

EvTable44. Study results: Nicergoline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point] (specify)**		**Final] (specify) 8 w**	
Saletu 1995	OC Analysis 1] Placebo (SDAT) 2] Nicergoline 30 mg bid (SDAT) 3] Placebo (MID) 4] Nicergoline 30 mg bid (MID) 5] Placebo change from baseline (SDAT) 6] Nicergoline change from baseline (SDAT) 7] Placebo change from baseline (MID) 8] Nicergoline change from baseline (MID) 9] Placebo vs Nicergoline change from baseline (SDAT) 10] Placebo vs Nicergoline change from baseline (MID)	CGI(Item 1) CGI(Item 2) SCAG total MMSE HAM-D NOSIE	1] 4.29 (0.95) 2] 4.33 (1.01) 3] 4.23 (1.03) 4] 4.42 (1.02) 1] 55.2 (13.4) 2] 56.8 (15.5) 3] 54.3 (13.8) 4] 55.8 (16.1) 1] 21.8 (4.8) 2] 21.5 (3.1) 3] 22.0 (3.4) 4] 22.1 (3.0)				1] 4.04 (0.95) 2] 3.54 (0.88) 3] 4.00 (1.17) 4] 3.83 (1.09) 1] 3.75 (0.61) 2] 3.21 (0.78) 3] 3.81 (0.57) 4] 3.29 (0.62) 1] 51.5 (11.0) 2] 46.6 (11.4) 3] 50.1 (14.3) 4] 49.1 (15.9) 1] 24.0 (5.3) 2] 25.7 (3.5) 3] 22.9 (5.4) 4] 25.8 (3.7)	5] <0.05 6] <0.001 7] <0.03 8] <0.001 9] <0.025 10] <0.05 9] 0.001 10] 0.04 5] <0.05 6] <0.01 7] NS 8] NS 9] <0.01 10] <0.05 5] <0.01 6] <0.01 7] NS 8] <0.01 9] <0.01 10] <0.01 9] NS 10] NS 9] NS 10] NS

EvTable45. Study results: Nicergoline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3m**		**Final: (specify) 6m**	
Winblad, 2001a	ITT Analysis 1] Placebo 2] Nicergoline 30mg bid 3] Placebo change from baseline 4] Nicergoline change from baseline 5] Nicergoline change from Placebo	 <u>CGIC</u> <u>Informant rated</u> CGIC Patient rated <u>ADAS-Cog</u> ADAS-Noncog ADAS-Total IADL PSMS	 1] 18.6 (6.6) 2] 18.3 (6.9) 1] 9.5 (3.8) 2] 9.6 (3.5)		 1] 4.26 2] 4.08 1] 4.07 2] 3.91		 1] 4.39 2] 4.32 1] 4.16 2] 4.09 3] 1.38 (0.57)* 4]-0.17 (0.55)* 5] 1.55 3] 0.75 (0.26)* 4] 0.14 (0.26)* 5] 0.61 3] 1.93 (0.68)* 4]-0.08 (0.65)* 5] 2.01 3] 1.47 (0.34) 4] 1.13 (0.33) 3] 1.07 (0.19) 4] 0.84 (0.19)	 5] NS 5] NS 3] <0.01 4] NS 5] <0.05 3] <0.01 4] NS 5] <0.1 3] NS 4] <0.01 5] <0.05 5] NS 5] NS

*SEM

EvTable46. Study results: Nicergoline - Antagonic Stress.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 3m**	
Schneider 1994	OC Analysis 1] Nicergoline 20 mg tid 2] Antagonic Stress 3 capsules tid 3] Nicergoline change from baseline 4] Antagonic Stress change from baseline 5] Difference between Nicergoline and Antagonic Stress in change from baseline	SCAG SASG WAIS Digit symbol	1] 66.5 (11.5) 2] 71.2 (7.7) 1] 65.8 (9.5) 2] 68.4 (8.9) 1] 7.8 (1.2) 2] 7.5 (1.6)				1] 50.5 (8.6) 2] 46.1 (6.5) 1] 52.1 (9.4) 2] 47.3 (6.5) 1] 9.6 (1.6) 2] 11.5 (2.4)	3] <0.001 4] <0.001 5] 0.002 favors AS 3] <0.001 4] <0.001 5] 0.000 favors AS 3] <0.001 4] <0.001 5] 0.000 favors AS

EvTable47. Adverse Events: Nicergoline.

Adverse events (AE) identified in included studies	Hermann, 1997	Nappi, 1997	Saletu, 1995	Winblad, 2001a	NICERGOLINE ANTAGONIC STRESS Schneider, 1994
Withdrawn (%) due to AE	T: 1 C: 3	T: 0 C: 0	T: 2 C: 2	T: 9 C: 8	T: NR C: NR
AE Checklist (Max 5)	2	4	5	3	0
None Reported					x
Balance					
Accidental Injury					
Dizziness	x		x		
Falls					
Behavioral					
Agitation	x			x	
Cardiovascular	x				
Arrhythmia	x		x		
Hypotension					
Hypertension					
Extrapyramidal	x				
Tremor					
Gastrointestinal	x	x		x	
Abdominal pain					
Constipation	x		x		
Diarrhea	x		x		
Dyspepsia	x				
Nausea, vomiting	x				
Metabolic/nutritional				x	
Eating disorder	x				
Weight Change			x		
Neurological				x	
Asthenia					
Psychiatric				x	
Anxiety	x				
Confusion, delirium					
Depression	x		x		
Respiratory					
Cough, cold, infection	x				
Rhinitis	x		x		
Other	x	x	x		
Aberrant hematology					
Fatigue, weakness	x				
Fever, flu, pneumonia	x				
Headache	x	x	x	x	
Hepatic abnormality					
Muscle/joint disorder	x				
Pain	x				
Rash, skin disorder	x		x		
Sleep disorder	x		x	x	
Urinary disorder				x	

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable48. Key characteristics: Physostigmine.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Moller 1999	NR	6	Placebo Physostigmine	DSM-III-R NINCDS	AD	Mild-Mod	181	143	69.3y (50-85y) 48%M	30 and 60 mg patch	24w	ADAS CGIC HAM-D HIS MMSE NOSGER	No
Thal 1996b	IS PI	6	Placebo Physostigmine	NINCDS	AD	Probable	366	333	68.6y (47-87y) 51%M 97% White	Titration: 9, 12, 15 mg bid, increased weekly	6w	ADAS-Cog CGI-C IADL MMSE PSMS	No
Thal 1999	IF	5	Placebo Physostigmine	NINCDS	AD	Probable	475	210	73.4y range 51-92 39.8% M 91% White 80% High School Grads Community	2w washout Titration: 9mg bid, 12mg bid, 15mg bid 24w drug in increased every 3w week 9 to 24 30mg/d or 36mg/d	24w	ADAS-Cog GERRI IADL CIBIC+ CGIC	No

EvTable48. Key characteristics: Physostigmine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	#Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
VanDyck 2000	IF	7	Placebo Physostigmine	NINCDS	AD	Probable Mild-Mod	176	148	71.5y (44-88y) 63%M 95 % White 4 %Black 1% Hispanic	30 mg/d (15 mg bid)	12w	ADAS-Cog CIBIC+ CIBIC CGIC IADL MMSE	No

EvTable49. Study results: Physostigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 24 w**	
Moller, 1999	OC Analysis 1] Placebo 2] Physostigmine 30 mg patch 3] Physostigmine 60 mg patch 4] Treatment vs Placebo from baseline	ADAS-Cog ADAS-Noncog ADAS-Total NOSGER CGIC % improved	1] 28.5 2] 29.8 3] 30.8 1] 7.7 2] 7.5 3] 6.9 1] 36.2 2] 37.3 3] 37.6 1] 68.8 2] 67.5 3] 66.6				1] 27.1 2] 31.4 3] 31.3 1] 6.6 2] 7.0 3] 6.5 1] 33.7 2] 38.4 3] 37.9 1] 68.8 2] 72.0 3] 38.8 1] 47% 2] 36% 3] 21%	 4] NS

EvTable50. Study results: Physostigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Thal 1996b	ITT Analysis 1] Placebo difference from baseline 2] Physostigmine 15 mg best dose difference from baseline 3] Difference between change from baseline between placebo and Physostigmine	<u>ADAS-Cog</u> <u>CGIC</u> MMSE PSMS IADL					1] 0.63 2] -1.12 1] -0.04 2] 0.22 1] -0.60 2] 0.05 1] 0.14 2] 0.33 1] 4.13 2] 1.67	3] 0.003 3] 0.0120 3] 0.132 3] 0.383 3] 0.101

EvTable51. Study results: Physostigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 24 w**	
Thal 1999	ITT Analysis (LOCF) 1] Placebo 2] Physostigmine Controlled-release 15mg bid DIFFERENCE FROM PLACEBO 3] Physostigmine Controlled-release 18mg bid DIFFERENCE FROM PLACEBO	<u>ADAS-cog</u> <u>CIBIC+</u> CGIC GERRI IADL					2] –2.9 3] –2.9 2] 0.31 3] 0.26 2] 0.16 3] 0.24 2] –0.07 3] –0.03 2] –3.85 3] –0.10	2] 0.002 3] 0.001 2] 0.019 3] 0.042 2] NS 3] NS 2] NS 3] NS 2] NS 3] NS

EvTable52. Study results: Physostigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
Van Dyck 2000	ITT Analysis 1] Placebo change from baseline 2] Physostigmine 12 or 15 mg BID change from baseline 3] difference between Placebo and Physostigmine in change from baseline	<u>ADAS-Cog</u> <u>CIBIC+</u> <u>CGIC</u> MMSE IADL					1] 1.06 (5.17) 2] -0.96 (5.22) 1] -0.33 (0.82) 2] 0.00 (0.88) 1] -0.30 (0.84) 2] -0.12 (0.87) 1] -0.87 (3.20) 2] -0.25 (2.98) 1] 3.51 (12.54) 2] 1.28 (12.48)	3] 0.01 3] 0.02 3] 0.17 3] 0.22 3] 0.25

EvTable53. Adverse Events: Physostigmine.

Adverse events (AE) identified in included studies	Moller, 1999	Thal, 1996b	Thal, 1999	Van Dyck, 2000
Withdrawn (%) due to AE	T: 12 C: 1	T: 16 C: 5	T: 55 C: 5	T: NR C: NR
AE Checklist (Max 5)	1	2	2	2
None Reported				
Balance				X
Accidental Injury			X	X
Dizziness		X		S
Falls				
Behavioral				
Agitation			X	X
Cardiovascular				
Arrhythmia				
Hypotension				
Hypertension				
Extrapyramidal				
Tremor	X	X		S
Gastrointestinal	X		X	X
Abdominal pain	X	X	X	X
Constipation				
Diarrhea		X	X	X
Dyspepsia			X	X
Nausea, vomiting	X	X	X	X
Metabolic/nutritional		X		
Eating disorder		X	X	X
Weight Change				S
Neurological				
Asthenia		X	X	S
Psychiatric				
Anxiety				X
Confusion, delirium				S
Depression				
Respiratory				S
Cough, cold, infection				
Rhinitis				
Other	X	X	X	S
Aberrant hematology				
Fatigue, weakness				
Fever, flu, pneumonia				
Headache	X	X		X
Hepatic abnormality				
Muscle/joint disorder				X
Pain				X
Rash, skin disorder	X			
Sleep disorder			X	X
Urinary disorder				

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable54. Key characteristics: Posatirelin.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Ferrari 1998	NR	5	Placebo Posatirelin	DSM-III-R ICD-10 NINCDS	AD PDD VaD	Probable	213	172	78.8y (≥65y) 42%M	10 mg/d	3m	GBS GDS HDRS HIS MMSE RMT	AD vs Vad
Gasbarrini 1997	NR	6	Placebo Posatirelin	NINCDS NINDS-AIREN	AD VaD	Probable Mild-Mod	360	357	77.6y (≥60y) 38%M	10mg/d	3m	GBS Laboratory tests Rey Memory Test	No
Parnetti 1996	PI	7	Placebo Posatirelin	NINDS-AIREN	VaD	Probable	136	105	69.4y (60-75y) 66%M comorbity: hypertension	10 mg ml/d	12w	GBS Laboratory tests RMT TPAT	No
Parnetti 1995	NR	6	Placebo Posatirelin Citicoline	NINCDS	AD	Probable Mild-Mod	222	214	74.9y (65-85y) 34%M	10 mg/d 500 mg/d	3m	GBS GDS HDRS MMSE Laboratory tests	No

EvTable55. Study results: Posatirelin.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 3m**	
Ferrari, 1998	ITT population (LOCF) 1] Placebo change from baseline (ALL) 2]: Posatirelin 10mg/ml IM change from baseline (ALL) 3] Posatirelin vs. Placebo change from baseline 4] Placebo change from baseline (AD) 5] Posatirelin 10mg/ml IM change from baseline (AD) 6] Posatirelin Placebo change from baseline (AD) 7] Placebo change from baseline (VaD) 8] Posatirelin 10 mg/ml IM change from baseline (VaD) 9] Posatirelin vs. Placebo change from baseline (VaD)	GBS Rating Scale Total score GBS Rating Scale motor function GBS Rating Scale intellectual GBS Rating Scale emotional				7] 1.5 (2.5) 8] –17.4 (5.8) 7] –0.4 (1.2) 8] –8.8 (3.1) 7] –0.4 (1.2) 8] –8.8 (3.1)	1] 1.1 (2.0)* 2] -9.2 (3.4)* 4] 0.3 (3.2) 5] -2.2 (3.6) 1] 0.9 (0.5)* 2] -1.5 (0.7)* 4] -0.4 (1.6) 5] -0.6 (0.9) 1] -0.4 (0.9)* 2] -4.5 (1.8)* 4] -0.4 (1.6) 5] -0.9 (1.9) 1] -0.04 (0.3)* 2] -0.7 (0.4)* 4] 0.0 (0.4) 5] -0.03 (0.4) 7] -0.1 (0.4) 8] -1.6 (0.7)	3]<0.001 3] 0.010 3] 0.005 3] 0.078

* SEM

EvTable56. Study results: Posatirelin.

Author Year	Outcome Measures	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 45d**		**Final: (specify) 90d**	
Gasbarrini 1997	ITT Population 1] Placebo 2] Posatirelin 10mg/d IM 3] difference between Placebo and Posatirelin from baseline	<u>GBS motor impairment</u>	1] 12.2(7.7) 2] 12.1(7.7)		1] 11.8(7.3) 2] 11.1(7.4)		1] 11.9(7.6) 2] 10.5(7.6)	3] <0.001
		<u>GBS intellectual impairment</u>	1] 25.9(10.7) 2] 25.7(10.7)		1] 25(10.7) 2] 23.6(10.2)		1] 24.5(11.4) 2] 21.9(10.7)	3] <0.001
		<u>GBS emotional impairment</u>	1] 7.4(3.6) 2] 7.4(3.6)		1] 7.1(3.6) 2] 6.6(3.4)		1] 6.9(3.8) 2] 6.1(3.5)	3] <0.001
		GBS Factor I	1] 11.6 (5.1) 2] 11.6 (5.0)		1] 11.3 (5.2) 2] 10.7 (4.6)		1] 11.2 (5.6) 2] 9.9 (4.9)	3] <0.001
		GBS Factor II	1] 12.2 (7.7) 2] 12.1 (7.7)		1] 11.8 (7.3) 2] 11.1 (7.4)		1] 11.9 (7.6) 2] 10.5 (7.6)	3] <0.001
		GBS Factor III	1] 6.1 (3.2) 2] 6.4 (3.2)		1] 6.1 (3.2) 2] 5.8 (3.3)		1] 5.9 (3.2) 2] 5.4 (3.3)	3] <0.001
		GBS Factor IV	1] 19.3 (8.3) 2] 19.4 (8.3)		1] 18.6 (8.4) 2] 17.5 (8.3)		1] 18.1 (8.9) 2] 16.2 (8.6)	3] <0.001

EvTable57. Study results: Posatirelin.

Author Year	Analysis Groups	Outcome Measures	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 45d		Final: (specify) 90d	
Parnetti, 1996	OC Population 1] Placebo 2] Posatirelin 10mg/ml 3] Posatirelin 10mg/ml vs Placebo change from baseline	GBS-ADL	1] 7.8 (5.1) 2] 8.5 (5.1)		1] 8.0 (5.2) 2] 7.5 (5.8)		1] 7.9 (5.0) 2] 7.0 (5.1)	3] 0.001
		GBS Emotional Impairment	1] 6.1 (2.3) 2] 5.6 (2.4)		1] 5.9 (2.4) 2] 4.8 (2.3)		1] 5.7 (2.6) 2] 4.3 (2.1)	3] 0.066
		GBS Motor impairment	1] 7.9 (5.1) 2] 8.5 (5.1)		1] 8.0 (5.2) 2] 7.5 (4.8)		1] 7.9 (5.0) 2] 7.1 (5.1)	3] 0.001
		GBS Intellectual impairment	1] 19.8 (8.9) 2] 20.3 (8.8)		1] 19.9 (9.3) 2] 16.1 (7.2)		1] 20.4 (9.6) 2] 14.7 (7.5)	3]<0.001
		TP Global	1] 0.6 (0.4) 2] 0.7 (0.4)		1] 0.7 (0.4) 2] 0.8 (0.5)		1] 0.6 (0.4) 2] 0.9 (0.5)	3] 0.076
		Randt acquisition	1] 65.1 (13.0) 2] 64.2 (10.0)		1] 63.4 (2.3) 2] 69.0 (10.1)		1] 63.1 (12.9) 2] 70.3 (11.2)	3] <0.001
		Randt recall	1] 64.8 (23.7) 2] 66.7 (25.5)		1] 61.4 (24.3) 2] 67.5 (23.1)		1] 63.0 (26.9) 2] 72.2 (26.8)	3] 0.058
		Randt memory	1] 60.8 (20.8) 2] 60.5 (18.8)		1] 57.0 (18.9) 2] 63.5 (16.0)		1] 57.7 (21.4) 2] 67.1 (19.0)	3] <0.001

EvTable58. Study results: Citicoline - Posatirelin.

Author Year	Analysis Groups	Outcome s Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 45 d**		**Final: (specify) 90 d**	
Parnetti 1995	OC Population 1] Placebo (Ascorbic Acid 100 mg/d) 2] Citicoline 500 mg/d 3] Posatirelin 10 mg/d 4] Ascorbic Acid change from baseline 5] Citicoline change from baseline 6] Posatirelin change from baseline 7] Posatirelin vs Citicoline change from baseline	GBS Emotional impairment GBS Impaired orientation & memory GBS Impaired ability ADL GBS Depression / Anxiety GBS Impaired attention & motivation GBS Intellectual impairment GBS Motor impairment MMSE HDRS	1] 1.9 (1.0) 2] 1.9 (1.0) 3] 1.9 (1.2) 1] 2.2 (0.9) 2] 2.2 (1.0) 3] 2.1 (1.0) 1] 1.2 (0.8) 2] 1.4 (1.1) 3} 1.2 (1.0) 1] 1.5 (0.9) 2] 1.5 (0.8) 3] 1.6 (1.1) 1] 2.2 (0.9) 2] 2.1 (1.0) 3] 2.1 (1.1) 1] 2.2 (0.8) 2] 2.1 (0.9) 3] 2.0 (0.9) 1] 1.2 (0.8) 2] 1.4 (1.1) 1] 16.4 (2.7) 2] 16.5 (2.6) 3] 16.6 (2.5) 1] 13.0 (5.0) 2] 11.4 (4.9) 3] 12.6 (5.0)		1] 1.8 (1.0) 2] 1.9 (1.1) 3] 1.7 (1.0) 1] 2.1 (1.0) 2] 2.1 (1.0) 3] 2.0 (1.0) 1] 1.3 (0.8) 2] 1.3 (1.0) 3] 1.1 (1.0) 1] 1.5 (0.9) 2] 1.5 (0.9) 3] 1.5 (1.0) 1] 2.1 (0.9) 2] 2.0 (1.0) 3] 1.9 (0.9) 1] 2.1 (0.9) 2] 2.0 (0.9) 3] 1.9 (0.9) 1] 1.3 (0.8) 2] 1.3 (1.0) 3] 1.1 (1.0)		1] 1.9 (1.0) 2] 1.7 (1.0) 3] 1.6 (0.9) 1] 2.1 (1.1) 2] 2.1 (1.0) 3} 1.8 (1.0) 1] 1.3 (0.9) 2] 1.4 (1.0) 3] 1.1 (1.0) 1] 1.4 (0.9) 2] 1.4 (0.9) 3] 1.4 (0.9) 1] 2.1 (1.0) 2] 1.9 (1.0) 3] 1.8 (0.8) 1] 2.1 (1.0) 2] 2.0 (0.9) 3] 1.8 (0.8) 1] 1.3 (0,9) 2] 1.4 (1.0) 3] 1.1 (1.0) 1] 17.1 (4.1) 2] 17.6 (3.9) 3] 17.8 (3.4) 1] 11.4 (4.9) 2] 11.3 (5.2) 3] 11.1 (5.3)	4] NS 5] NS 6] <0.025 4] NS 5] NS 6] NS 7] 0.038 favors Posatirelin 4] NS 5] NS 6] <0.025 4] NS 5] NS 6] NS 7] 0.031 favors Posatirelin 4] NS 5] NS 6] <0.025 5] <0.025 7] 0.037 favors Posatirelin 5] <0.025 4] NS 5] NS 6] NS 4] NS 5] NS 6] NS

EvTable59. Adverse Events: Posatirelin.

Adverse events (AE) identified in included studies	Ferrari, 1998	Gasbarrini, 1997	Parnetti, 1995	Parnetti, 1996
Withdrawn (%) due to AE	T: 4 C: 3	T: 3 C: 1	T: 0 C: 0	T: NR C: NR
AE Checklist (Max 5)	3	4	4	2
None Reported				
Balance	X			
Accidental Injury				
Dizziness	X	X		
Falls				
Behavioral				
Agitation	X	X	X	X
Cardiovascular				
Arrhythmia	X		X	X
Hypotension				
Hypertension		X		
Extrapyramidal				
Tremor			X	X
Gastrointestinal				X
Abdominal pain	X			
Constipation				
Diarrhea		X		
Dyspepsia			X	
Nausea, vomiting	X	X		X
Metabolic/nutritional		X		
Eating disorder				
Weight Change				
Neurological				
Asthenia				X
Psychiatric				
Anxiety				
Confusion, delirium			X	
Depression				
Respiratory				
Cough, cold, infection				
Rhinitis				
Other		X	X	X
Aberrant hematology		X		
Fatigue, weakness				
Fever, flu, pneumonia				
Headache	X	X	X	
Hepatic abnormality				
Muscle/joint disorder		X		
Pain				
Rash, skin disorder	X	X	X	
Sleep disorder	X		X	X
Urinary disorder		X	X	

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable60. Key characteristics: Rivastigmine.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Agid 1998	IF	7	Placebo Rivastigmine	DSM-III-R NINCDS	Dementia AD	Mild-Mod Probable	386	357	69.4y (50-90y) 44%M	Titration: 3 w Then 4 or 6 mg/d	15w	Benton Visual Retention CGIC Digit Symbol Substitution ECG Fuld Object-Memory Laboratory tests MMSE NOSGER Trail Making	No
Corey-Bloom 1998 Auxiliary: Farlow 2001 Farlow 2000 Kumar 2000 Del Ser 2000 Doraiswamy 2002	IF	8	Placebo Rivastigmine	DSM-IV NINCDS	AD	Mild-Modly Sev	699	545	74.5y (45-89y) 39%M 93% of patients were taking medications for other conditions: cardiovascular (43%), gastro (59%) analgesics (56%) 95% White	Titration: w 1-7; Then dose range: 1 –6 mg/d	26w	ADAS-Cog CIBIC+ GDS MMSE PDS	Vascular Risk (HIS)

EvTable60. Key characteristics: Rivastigmine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Forette 1999	IF	6	Placebo Rivastigmine	NINCDS DSM-III-R	DAT	Mild-Mod	114	85	70.6y (NR) %M NR	Titration: 2 mg/d, 3 mg/d at d 4, increment of 0.5 mg q4d until d 28 and increment of 1 mg qw 12 mg/d	18w	ADAS-cog CIBIC+ Digit span test ECG Laboratory tests NOSGER Wechsler logical memory test	No
McKeith 2000	IF	8	Placebo Rivastigmine	Consensus Criteria	Lewy-body Dementia	Mild-Mod	120	92	73.9y (57-87y) 56%M	Titration: 1.5 mg bid for 2 w up to 6 mg bid	20w	CGC-plus ECG Laboratory tests MMSE NPI NPI-10 NPI-4 UPDRS	No
Potkin 2001	PI	5	Placebo Rivastigmine	DSM IV NINCDS	AD	Mild-Modly Sev	27	27	75.9y (64-89y) %M NR	Titration over a period of 12 w then 3, 6, or 9 mg/d	26w	CIBIC+ FDG-PET scan MMSE MRI Snodgross Picture Naming Task	No

EvTable60. Key characteristics: Rivastigmine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Rosler 1999 AUXILIARY Rosler 2001 Farlow 2000 Rosler 1998 Doraiswamy 2002	IF	8	Placebo Rivastigmine	DSM IV NINCDS	AD	Mild-Modly Sev	725	581	72y (45-95y) 41%M Community. Comorbidity: diabetes, hypertension, arthritis	Titration on w 1 to 12 with increments of 1.5 mg/d4 mg/d 12 mg/d	14w	ADAS-Cog CIBIC CIBIC Progressive Deterioration scale Global Deterioration scale MMSE	No

EvTable61. Study results: Rivastigmine.

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 7w**		**Final: (specify) 13w**	
AGID 1998	Observed Cases 1] Placebo 2] Rivastigmine 4 mg BID 3] Rivastigmine 6 mg BID 4] Rivastigmine 4 mg bid versus Placebo change from baseline 5] Rivastigmine 6 mg bid versus Placebo change from baseline 6] Placebo change from baseline 7] Rivastigmine 4 mg bid change from baseline 8] Rivastigmine 6 mg bid change from baseline	CGIC Successful outcome Digit Symbol Substitution MMSE Trail Making NOSGER IADL NOSGER Mood, memory, self-care, social behavior, disturbing behavior			6] 0.1(7.4) 7] 2.1(5.8) 8] 2.0(5.4) 6] -0.6(31.2) 7] -4.3(36.9) 8] -5.4(45.3)	5] <0.005	1] 29.91% 2] 31.53% 3] 42.72% 6] 0.5(6.9) 7] 1.7(5.1) 8] 2.8(8.1) 6] 0.0(2.6) 7] 0.0(3.3) 8] 0.3(3.1) 6] 0.5(28.7) 7] -1.6(39.0) 8] -7.3(48.9) 6] –0.2 (3.3) 7] 0.0 (3.3) 8] –0.7 (3.5)	5] <0.05 4] NS 5] <0.05 4] NS 5] NS 4] NS 5] NS

EvTable61. Study results: Rivastigmine cont'd.

REF ID#	Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		**Mid-Point: (specify) 7w**		**Final: (specify) 13w**	
			FULD Object-Memory Evaluation (TS)			6] 0.0 (6.2) 7] 2.2 (7.3) 8] 2.0 (6.6)	4] <0.01 5] <0.05	6] –0.9 (5.5) 7] –0.4 (6.2) 8] 0.7 (6.2)	4] <0.05 5] <0.05
			FULD Object-Memory Evaluation (TR)			6] 0.5(4.6) 7] 1.7 (5.3) 8] 2.4 (4.8)	4] <0.05 5] <0.005	6] 0.1 (4.3) 7] 0.8 (4.6) 8] 1.1 (4.2)	4] NS 5] <0.05

EvTable62. Study results: Rivastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 26w	
Corey-Bloom 1998 Farlow 2001 Farlow 2000 Kumar 2000 Delser 2000 Doraiswamy 2002	ITT Analysis 1] Placebo 2] Rivastigmine 1-4 mg/ d 3] Rivastigmine 6-12 mg/ d 4] Placebo change from baseline 5] Rivastigmine low dose change from baseline 6] Rivastigmine high dose change from baseline 7] Placebo vs Rivastigmine low dose 8] Placebo vs Rivastigmine high dose 9] Difference among groups	ADAS-Cog	1] 21.7 2] 22.4 3] 22.3				4] – 4.09 5] – 2.36 6] - 0.31	8] <0.001
		CIBIC+					4) 0.49 5) 0.23 6) 0.20	8] < 0.01
		PDS					4] –4.90 5] –5.19 6] – 1.52	8] < 0.001
		GDS	1] 3.9 2] 4.0 3] 4.0				4] –0.32 5] –0.16 6] –0.13	7] <0.05 8] < 0.030
		MMSE	1] 20 2] 19.5 3] 19.6	9] 0.481			4] –7.9 5] –0.35 6] 0.30	8]< 0.05

EvTable63. Study results: Rivastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 18 w	
Forette 1999	Completers Analysis 1] Placebo	ADAS-Cog	1] 21.7 (8) 2] 24.1 (11.6) 3] 23.2 (8.5)				4] 2 5] -2.75 6] 0.25	7] 0.054
	2] Rivastigmine 12 mg d variable bid	NOSGER Self-care					4] -0.3 (2.5) 5] -0.4 (2.0) 6} -0.6 (2.4)	8] NS
	3] Rivastigmine 12 mg d variable tid	NOSGER Disturbing behaviour					4] 0.1 (3.1) 5] -0.3 (2.1) 6] -0.7 (3.4)	8] NS
	4] Placebo mean change from baseline	NOSGER IADL					4] 0.8 (4.0) 5] 0.4 (3.1) 6] -0.7 (4.0)	8] NS
	5] Rivastigmine bid mean change from baseline	NOSGER Memory					4] 1.3 (3.7) 5] -0.7 (2.9) 6] -1.0 (2.7)	5] 0.037 6] 0.014 8] 0.032
	6] Rivastigmine tid mean change from baseline	NOSGER Mood					4] -0.6 (3.2) 5] 0.7 (3.0) 6] -0.4 (3.4)	8] NS
	7] Rivastigmine bid vs. placebo	NOSGER Social behaviour					4] 0.3 (3.3) 5] 0.0 (2.6) 6] -1.1 (3.8)	8] NS
	8] Rivastigmine bid & tid vs. placebo	CIBIC+ Improved					1] 16% 2] 57% 3] 36%	7] 0.027
		Wechsler logical memory test					5] 1.8 (2.3) 6] 0.1 (2.3)	8] 0.012 immediate recall only

EvTable64. Study results: Rivastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 20w**	
McKeith 2000	ITT Analysis 1] Placebo 2] Rivastigmine 12 mg d 3] Placebo mean change from baseline 4] Rivastigmine mean change from baseline 5] Rivastigmine versus placebo change from baseline	NPI-4	1] 11.7 (8.6) 2] 12.2 (8.2)				3] 0.8 (7.3) 4] 2.5 (8.4)	5] 0.088 CI (-1.1 – 4.6)
		NPI-10					3] 1.2 (10.7) 4] 5.0 (16.2)	5] 0.048 CI (-1.6 – 9.2)
		CCASSS				5] 0.01		5] 0.048
		CGC+						5] NS
		MMSE	1] 17.8 (4.4) 2] 17.9 (4.7)					5] NS

EvTable65. Study results: Rivastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 26 w**	
Potkin 2000	OC Population 1] Placebo 2] Rivastigmine 9 mg/d 3] Placebo vs. Rivastigmine 4] Rivastigmine metabolism change from baseline	Snodgrass Picture Naming task CIBIC+ Ratio stabilized					 1] 2/7 2] 15/20	3] NS 3] <0.03*

* Tested the difference between the placebo and treatment group that had deteriorated (CIBIC+ score 5-7) only

EvTable66. Study results: Rivastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 18w**		**Final: (specify) 26w**	
Rosler 1999 Rosler 2001 Farlow 2000 Rosler 1998 Dorais-wamy 2002	ITT Analysis 1] Placebo 2] Rivastigmine 1-4 mg/ d 3] Rivastigmine 6-12 mg/ d 4] Placebo change from baseline 5] Rivastigmine low dose change from baseline 6] Rivastigmine high dose change from baseline 7] Placebo vs Rivastigmine low dose 8] Placebo versus Rivastigmine high dose	ADAS-Cog ADAS COG >4 point improvement CIBIC CIBIC+ PDS GDS MMSE	1] 23.4 2] 23.9 3] 23.6 1] 54.1 2] 53.8 3] 55.2		4] 4.09 5] 4.06 6] 3.85		4] – 1.34 5] – 1.37 6] 0.26 1] 16% 2] 15% 3] 24% 4] 4.38 5] 4.24 6] 3.91 4] 4.34 5] 4.20 6] 3.93 4] -2.18 5] –3.37 6] 0.05 4] –0.26 5] –0.22 6] –0.06 4] –0.47 5] –0.62 6] 0.21	7] > 0.05 8] > 0.011 7] >0.05 8] <0.1 7] > 0.05 8] < 0.001 8] < 0.05 7] > 0.05 8] < 0.07 8] < 0.05 8] < 0.05

EvTable67. Adverse Events: Rivastigmine.

Adverse events (AE) identified in included studies	Agid, 1998	Corey-Bloom, 1998	Forette, 1999	McKeith, 2000	Potkin, 2001	Rosler, 1999
Withdrawn (%) due to AE	T: 11 C: 4	T: 18+ C: 7	T: 27 C: 4	T: 12 C: 11	T: NR C: NR	T: 15+ C: 7
AE Checklist (Max 5)	4	3	5	4	2	2
None Reported					X	
Balance						
Accidental Injury						
Dizziness	X	S*	X			X
Falls						
Behavioral						
Agitation				X		
Cardiovascular			NS	NS		
Arrhythmia						
Hypotension						
Hypertension		S*				
Extrapyramidal						
Tremor						
Gastrointestinal		S*				
Abdominal pain	X		X			X
Constipation						
Diarrhea	X					X
Dyspepsia		S*				
Nausea, vomiting	X	S*	X	S		S*
Metabolic/nutritional						
Eating disorder		S*	X	S		X
Weight Change		S*	X	X		
Neurological		S*	X			
Asthenia		S*				
Psychiatric						
Anxiety						
Confusion, delirium						
Depression						
Respiratory						
Cough, cold, infection						
Rhinitis						
Other		S*	X			X
Aberrant hematology	NS*		NS	NS		
Fatigue, weakness		S*				X
Fever, flu, pneumonia						
Headache	X		X			X
Hepatic abnormality	NS*					
Muscle/joint disorder						
Pain						
Rash, skin disorder						
Sleep disorder		S*		S		
Urinary disorder						

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable68. Key characteristics: Tacrine.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	#Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Allain 1999	NR	7	Tacrine + Placebo Tacrine + Silymarin	NINCDS DSM-III-R	AD	Mild-Mod	222	194	74.2y (NR) 39%M Community All subjects + Tacrine	420 mg/d	15w	MMSE SKT	No
Gutzmann 2002	PI	7	Idebenone Tacrine	NINCDS DSM-III-R	AD PDD	Mild-Mod	203	44	71.2y (44-90y) 36%M 100% White 100% Community	360 mg/d 160 mg/d	60w	ADAS-Cog ADAS-Noncog ADAS-Total CGI CT EIS HIS MRI NOSGER-IADL	No

EvTable68. Key characteristics: Tacrine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Knapp 1994b Auxiliary: Farlow 1998, Schneider 1997, Raskind 1997, Henke 1997, Schneider 1996, Knopman 1996, Gracon 1996, Smith 1996, Knapp 1994	IF	7	Placebo Tacrine	NINCDS	AD	Probable Mild-Mod	663	279	72.8y (49-95y) 48%M	Titration: Group1-40 mg/d for 6w then 80 mg/d for 24w Group2-40 mg/d for 6w then 80 mg/d for 6w then 120 mg/d for 18w Group3-40 mg/d for 6w then 80 mg/d for 6w then 120 mg/d for 6w then 160 mg/d for 12w	30w	ADAS-Cog ADAS-Noncog ADAS-Total GDS CIBI FCCA GDS IADL MMSE PDS PSMS	ERT APOE Genotype Gender

EvTable68. Key characteristics: Tacrine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Maltby 1994	NI	6	Placebo Tacrine + Lecithin	NINCDS DSM-III-R	AD	Probable Mild-Mod	41	32	68.8y (52-84y) 51%M 100% Community	Tacrine: Started at 25 mg/d and doses increased by 25 mg q2w up to 100 mg/d	36w	Activities of daily living Carer Stress Assessment Cholinergic sensitive test Extrapyramidal score Digit Span Face recognition GDS LFT-Liver function test London psychogeriatric rating scale MMSE Mood states scale National adult reading test Neurological exam Selective reminding test Symptoms of stress Verbal Fluency Walsh tests	No
Prentice 1996	NI PI	5	Placebo Tacrine	DSM-III-R NINCDS	AD	Probable	23	19	68.0y (NR) 13%M	40 mg/d for 6 w, then 80 mg/d for 6 w	13w	CAMCOG CAMTOT MMSE Rivermead Behavioral Memory Test – Profile RPT Score SPET Scan	No

EvTable68. Key characteristics: Tacrine cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Weinstein 1991 Auxiliary: Goad 1991	NI IS	7	Placebo THA & Lecithin	DSM-III-R	AD	Probable	13	12	74.6y (56-79y) 50%M 100% Community	Titration: increments of 25 mg/d for 4 w, then 100 mg/d 10 g/d	12w	Burden Scale CAMCOG CAMDEX CT HDRS IDDD Laboratory tests MMSE	No
Wong 1999	IS	5	Placebo Tacrine	NINCDS	AD	Probable Mild-Mod	100	94	73.8y (52-94y) 50%M	30 mg/d for 6 w, 60 mg/d for 6 w, 90 mg/d for 6 w, then 120 mg/d	30w	CGIC CASI IQCODE ADS MMSE FCCA HIS	No
Wood 1994	IF	6	Placebo Tacrine	NINCDS	AD	Mild-Mod	154	131	75y (NR) 54%M 100% Community	Titration: 20 mg/bid for 2 d, 20 mg/tid for 2 d 40 mg bid for 7 d. Then the dose could be increased or decreased in 20 mg amount to reach optimum dose. Max dose: 120 mg/d	12w	ADAS-Noncog AMTS Blessed Scale CGRS GBS LFT-Liver function test Mann-Whitney test MMSE RGRS Rosen	No

EvTable69. Study results: Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 15w**	
Allain 1999	ITT Analysis 1] Placebo + Tacrine 80mg qid 2] Silymarin 140mg tid + Tacrine 80 mg qid	<u>SKT</u> <u>MMSE</u>	1] 17.2 (6.1) 2] 17.6 (6.1) 1] 17.8 (4.4) 2] 17.1 (4.2)				1] 17.4 (6.3) 2] 18.2 (6.6) 1] 18.3 (5.4) 2] 17.3 (5.3)	1] NS 2] NS 1] NS 2] NS

EvTable70. Study results: Idebenone-Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 60 w**	
Gutzmann 2002	ITT Analysis 1] Idebenone 360 mg d 2] Tacrine 160 mg d variable 3] Difference between Idebenone and Tacrine	EIS% Rating = -1 Rating = 0 Rating = 1 Rating = 2 Rating = 3 ADAS-Total ADAS-Cog ADAS-Noncog CGI-S NOSGER-IADL	 1] 41.55(16.46) 2] 41.52(14.92) 1] 30.23(11.59) 2] 30.93(10.59) 1] 11.32 (6.79) 2] 10.55(5.86) 1] 5.22 (0.46) 2] 5.19 (0.44) 1] 13.88(4.43) 2] 13.78(4.55)				1] 28.9% 2] 9.0% 1] 54.8% 2] 83.8% 1] 16.3% 2] 7.1% 1] 13.5% 2] 3.0% 1] 8.7% 2] 4.0% 1] 6.7% 2] 2.0% 1] 34.51(17.43) 2] 30.44(16.32) 1] 26.40(16.67) 2] 24.81(14.92) 1] 8.11(7.56) 2] 5.63(6.10) 1] 4.43 (1.58) 2] 4.53 (1.45) 1] 13.13 (5.49) 2] 12.5 (6.25)	 3] <0.0001 favours Idebenone 3] NS 3] NS 3] NS

EvTable71. Study results: Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 30w	
Knapp 1994	ITT Analysis 1] Placebo 2] Tacrine 80mg/d 3] Tacrine 120mg/d 4] Tacrine 160mg/d variable 5] Tacrine 80mg/d versus Placebo 6] Tacrine 120mg/d versus Placebo 7] Tacrine 160mg/d variable versus Placebo	CIBI ADAS-Cog FCCA (% improved) GDS ADAS-Noncog ADAS-Total MMSE					1] 19% improved 4] 41% improved 5] -0.01 CI (-0.4-0.1) 6] -0.02 CI (-0.4 -0.006) 7] 0.2 CI (-0.4 - -0.01) 1] 29.2 (11.8) 2] 30.9 (13.4) 3] 28.5 (11.1) 4] 28.0 (11.8) 5] -1.4 CI (-3.5-0.7) 6] -2.0 CI (-3.5 - -0.5) 7] -2.2 CI (-3.5 - -0.8) 1) 16% 4) 42% 5] 0.07 CI (-0.1-0.3) 6] -.05 CI (-0.2-0.08) 7] -0.2 CI (-0.3 - -0.04) 5] -0.8 CI (-2.2-0.6) 6] -0.3 CI (-1.3-0.7) 7] -0.7 CI (-1.6-0.2) 5] -2.4 CI (-5.2-0.4) 6]-2.2 CI (-4.2 - -0.3) 7] -3.0 CI (-4.8- -1.1) 1] 18.2 (5.0) 2] 17.1 (4.6) 3] 18.7 (4.6) 4] 18.8 (4.5) 5] 0.6 CI (-0.6-1.7) 6] 0.4 CI (-0.4 - -1.2) 7] 0.9 CI (0.1-1.6)	5] 0.33 6] 0.04 7] 0.04 5] 0.20 6] 0.008 7] 0.002 7) <0.002 5] 0.48 6] 0.47 7] 0.01 5] 0.26 6] 0.52 7] 0.12 5] 0.09 6] 0.03 7] 0.002 5] 0.33 6] 0.37 7] 0.02

EvTable72. Study results: Tacrine & Lethicin.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6 m**		**Final: (specify) 9 m**	
Maltby 1994	OC Population 1] Placebo & Lethicin 9X1200mg d 2] Tacrine 100 mg/d variable & Lethicin 9X1200mg d 3] Treatment effect Tacrine & Lethicin vs. Placebo & Lethicin	MMSE	1] 17.3 (6.7) 2] 16.6 (6.8)		1] 16.4 (6.8) 2] 16.1 (6.5)		1] 15.2 (8.0) 2] 14.4 (6.7)	3] 0.9444
		IADL	1] 10.3 (2.6) 2] 8.5 (2.5)		1] 9.5 (2.6) 2] 8.3 (2.8)		1] 9.6 (2.7) 2] 7.6 (3.4)	3] 0.622
		LPRS	1] 14.1 (7.7) 2] 15.2 (6.5)		1] 15.7 (10.9) 2] 18.2 (9.6)		1] 18.9 (12.1) 2] 19.5 (10.9)	3] 0.638
		Verbal (words)	1] 35.5 (15.9) 2] 34.9 (15.1)		1] 37.5 (16.0) 2] 38.7 (16.5)		1] 34.9 (16.3) 2] 38.5 (16.3)	3] 0.200
		Visual (objects)	1] 36.8 (21.2) 2] 30.7 (13.3)		1] 32.8 (22.8) 2] 31.4 (18.1)		1] 30.8 (22.7) 2] 26.2 16.9)	3] 0.359
		Digit forward	1] 5.9 (2.7) 2] 6.1 (2.8)		1] 5.2 (2.6) 2] 5.9 (2.4)			3] 0.723
		Verbal fluency	1] 22.4 (13.2) 2] 23.1 (15.0)		1] 19.8 (11.8) 2] 24.3 (14.8)			3] 0.198
		Face recognition	1] 3.8 (1.4) 2] 3.9 (2.0)		1] 3.4 (1.8) 2] 3.4 (1.2)			3] 0.651
		Carer stress assess.	1] 2.4 (4.4) 2] 4.0 (6.3)		1] 2.6 (4.9) 2] 2.0 (2.2)		1] 2.2 (3.9) 2] 3.1 (4.8)	3] 0.397

EvTable73. Study results: Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
Prentice 1996	OC Population 1] Placebo 2] Tacrine 40 mg/d 6w, then 80 mg/d 6w. 3] Placebo vs. Tacrine	MMSE CAMTOT RPT	1] 18.4 (6.7) 2] 14.9 (5.0) 1] 67.0 (12.5) 2] 53.5 (17.3) 1] 4.1 (3.7) 2] 4.1 (3.0)				1] 19.1 (7.0) 2] 15.7 (5.2) 1] 68.4 (18.0) 2] 54.7 (20.7) 1] 5.6 (4.7) 2] 3.6 (3.1)	3] NS 3] NS 3] NS

EvTable74. Study results: Tetrahydroaminoacridine & Lethicin.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
Weinstein 1990	OC Population 1] Placebo 2] Tetrahydro-aminoacridine (THA) 100 mg/d & Lethicin 10 g/d 3] THA vs. Placebo	CAMCOG IDDD Burden scale MMSE	1] 63 (12) 2] 44 (26)				1] 64 (16) 2] 45 (29)	3] NS 3] NS 3] NS 3] NS

EvTable75. Study results: Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 18w**		**Final: (specify) 30w**	
Wong 1998	ITT Analysis 1] Placebo 2] Tacrine 120 mg/d 3] Placebo mean change from baseline 4] Tacrine mean change from baseline 5] Tacrine vs. Placebo mean change from baseline	<u>CGIC</u> <u>CASI</u> <u>IQCODE</u> ADS MMSE	1] 17.9 (4.8) 2] 16.2 (4.8)				3] 0.05 4] 0.02 3] -3.60 4] –0.85 3] 2.95 4] 3.13 3] –1.00 4] –0.66 3] 1.50 4] –0.21	5] 0.802 5] 0.050 5] 0.835 5] 0.978 5] 0.057

EvTable76. Study results: Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12 w	
Wood 1994	ITT (LOCF) Analysis 1] Placebo 2] Tacrine 80 mg/d variable 3] Placebo least squares mean 4] Tacrine least squares mean 5] Tacrine vs. Placebo	<u>MMSE</u> <u>CGRS</u> RGRS Blessed GBS Adas-noncog AMTS					3] 18.44 (0.54)* 4] 18.82 (0.55)* 3] 4.89 (0.24)* 4] 4.73 (0.25)* 3] 31.70 (1.70)* 4] 29.10 (1.71)* 3] 8.11 (0.48)* 4] 7.97 (0.51)* 3] 4.87 (0.21)* 4] 5.21 (0.22)*	5] 0.55 5] 0.012 5] 0.03 5] 0.60 5] 0.20 5] 0.53 5] 0.18

* SEM

EvTable77. Adverse Events: Tacrine.

Adverse events (AE) identified in included studies	Knapp, 1994	Maltby, 1994	Prentice 1996	Weinstein, 1991	Wong, 1999	Wood, 1994	Tacrine+Silymarin (T) Tacrine+Placebo(C) Allain 1988	TACRINE (T) IDEBENONE (C) Gutzmann, 2002
Withdrawn (%) due to AE	T: 55 C:11	T: 43 C: 0	T: 0 C: 0	T: 14 C: 0	T: 27 C:12	T: 16 C: 5	T: 8 C: 8	T: 41 C: 17
AE Checklist (Max 5)	3	3	1	3	2	3	3	3
None Reported								
Balance								
Accidental Injury								
Dizziness	X				X	X		
Falls								
Behavioral		X					NS	
Agitation	X							
Cardiovascular								
Arrhythmia								
Hypotension								
Hypertension								
Extrapyramidal								
Tremor					X			
Gastrointestinal	X							S*
Abdominal pain	X				X			
Constipation								
Diarrhea	X				X	X	NS	
Dyspepsia	X							
Nausea, vomiting	X	X		X	X	X	NS	S*
Metabolic/nutritional								
Eating disorder	X				X		NS	
Weight Change	X							
Neurological			X					
Asthenia							NS	
Psychiatric								
Anxiety								
Confusion, delirium								
Depression		X						
Respiratory							NS	
Cough, cold, infection								
Rhinitis	X							
Other		X			X	X		
Aberrant hematology								
Fatigue, weakness							NS	
Fever, flu, pneumonia								
Headache	X					X		
Hepatic abnormality	X	X	X	X	X	X		S*
Muscle/joint disorder		X						
Pain								
Rash, skin disorder								
Sleep disorder							NS	
Urinary disorder		X				X		

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable78. Key characteristics: Velnacrine.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Antuono 1995	IF	7	Placebo Velnacrine	NINCDS	AD	Probable	449	280	72.8y (47-90y) 38%M	150 or 225 mg/d	24 w	ADAS-Cog CATS CGI-C PGR PSMS RAGS	No
Huff 1991	PI	6	Placebo HP 128 (Velnacrine)	NINCDS	AD	Probable	16	15	70.5y (46-84y) 31%M	100 mg bid	13d	ADAS Benton MAE CGI Plasma Levels RAGS Sentence Repetition Token Test Verbal Fluency Visual Naming	No
Zemlan 1996	IF	6	Placebo Velnacrine	NINCDS	AD	Probable	309	225	71.6y (51-89y) 41%M	10 mg, 25 mg, 50 mg or 75 mg tid	15w	ADAS-Cog CGI-C IADL PGIR PSMS	No

EvTable79. Study results: Velnacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 12w		Final: (specify) 24w	
Antuono 1995	LOCF Analysis 1] Placebo 2] Velnacrine 150 mg/d 3] Velnacrine 225 mg/d 4] Placebo change from baseline 5] Velnacrine 150 mg/d change from baseline 6] Velnacrine 225 mg/d change from baseline 7] Combined Velnacrine vs Placebo change from baseline 8] Velnacrine 150 mg/d vs Placebo change from baseline 9] Velnacrine 225 mg/d vs Placebo change from baseline	<u>ADAS-Cog estimate</u> <u>CGI-C estimate</u> PGIR PSMS RAGS CATS			4] -0.5 5] -0.5 6] -2.0 1] 4.1 2] 4.0 3] 3.8 1] 4.1 2] 3.9 3] 3.8 4] 0.62 5] -0.01 6] 0.30 4] 1.12 5] 0.46 6] 0.10	4] NS 5] NS 6] <0.001 4] 0.001 5] 0.001 6] 0.001	4] 1.5 5] 1.5 6] -1.0 1] 4.3 2] 4.1 3] 0.0 1] 4.4 2] 4.3 3] 3.9 4] 1.07 5] 0.49 6] 0.43 4] 2.68 5] 2.87 6] 1.55	7] NS 8] NS 9] <0.05 4] 0.001 5] 0.001 6] 0.001 7] 0.001 7] <0.05 7] <0.05 7] NS 8] NS 9] NS 7] <0.05 9] <0.01

EvTable80. Study results: HP 128 (Velnarcrine).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 10 d**	
Huff, 1991	OC Population 1] Placebo 2] HP 128 (Velnacrine) 100 mg bid 3] Placebo mean change from baseline 4] HP 128 mean change from baseline 5] HP 128 vs. placebo	ADAS MAE Controlled oral word association Visual naming Token test Sentence repetition test RAGS CGI					4] 0.3 4] 2.6 4] 3.0 4] 0.9 4] 0.0 3] 4.0 4] 3.3	5] NS 5] NS 5] NS 5] NS 5] NS 5] NS 5] >0.05

EvTable81. Study results: Velnacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 15w**	
Zemlan 1996	OC Analysis 1] Placebo 2] Velnacrine 75 mg tid best dose improvement relative to placebo	 ADAS-Cog CGI-Improvement ADAS-Total ADAS-Noncog PGIR CGI-Severity PSMS IADL					 2] 2.15 2] 0.25 2] 2.36 2] 0.03 2] 0.24 2] -0.01 2] 0.19 2] -0.28	 2] <0.001 2] 0.046 2] 0.001 2] 0.934 2] 0.073 2] 0.776 2] 0.294 2] 0.453

EvTable82. Adverse Events: Velnacrine.

Adverse events (AE) identified in included studies	Antuono, 1995	Huff, 1991	Zemlan, 1996
Withdrawn (%) due to AE	T: 5 C: 4	T: 8 C: 0	T: 33 C: 22
AE Checklist (Max 5)	3	3	3
None Reported			
Balance			
Accidental Injury			
Dizziness	X	X	
Falls			
Behavioral			
Agitation	X		
Cardiovascular			X
Arrhythmia		X	
Hypotension		X	
Hypertension		X	
Extrapyramidal			
Tremor			
Gastrointestinal		X	X
Abdominal pain			X
Constipation		X	
Diarrhea	X	X	X
Dyspepsia			
Nausea, vomiting	X	X	X
Metabolic/nutritional			
Eating disorder	X		X
Weight Change			
Neurological			
Asthenia			X
Psychiatric			
Anxiety			
Confusion, delirium			
Depression			
Respiratory			X
Cough, cold, infection			
Rhinitis			
Other	X		
Aberrant hematology	X		X
Fatigue, weakness			
Fever, flu, pneumonia			
Headache	X		
Hepatic abnormality	X		X
Muscle/joint disorder			
Pain			
Rash, skin disorder	X		X
Sleep disorder	X		
Urinary disorder			

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable83. Key Characteristics: Various cholinergic neurotransmitter modifying agents.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population (ethnicity, setting, comorbidity)	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Canal 1996	IF	6	Placebo Eptastigmine	NINCDS	AD	Mild-Mod	103	94	67.5y (48-85y) 49%M	20 mg bid (if ≤ 65 kg) 20 mg tid (if >65 kg)	4w	ADL CGI-C CGCI HAM-D IADL LMT Semantic Word Fluency Test Trail Making	No
Imbimbo 1999	IF	8	Placebo Eptastigmine	NINCDS DSM IV	AD	Mod-Modly Sev	491	424	71.0y (52-90y) 37%M 99% White	5 mg tid (start) 4-week step-wise increase to 15 mg tid & 20 mg tid	24w	ADAS-Cog CIBIC+ GDS HAM-D IADL	No
Xu 1995	IS	6	Placebo Huperzine	DSM-III-R	AD	Mild-Sev	103	103	66.0y (54-90y) 55%M Asian	1.6 mg/d	8w	ADL HDS HIS MMS MQ	No
Rockwood 1997 Auxiliary: Rockwood 2000	IF	7	Placebo Linopirdine	DSM-III-R NINCDS	AD	Mild-Mod	382	311	71.6y (NR) 44%M 98% White	30 mg tid	6m	ADAS-Total ADAS-Noncog ADAS-Cog CGI DBDS IADL MMSE PSMS A SKT	No
VanDyck 1997	PI	5	Placebo Linopirdine	NINCDS	AD	Mild-Mod	37	34	68.7y (NR) 54%M	40 mg tid	4w	ADAS-Cog CGIC DBDS	No

EvTable83. Key Characteristics: Various cholinergic neurotransmitter modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population (ethnicity, setting, comorbidity)	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Mohr 1997	NR	5	Placebo Sabeluzole	DSM-III-R NINCDS	AD	Mild-Mod	39	15	68.8y (53-79y) 49%M	10 mg bid	48w	ADAS-Cog CT Scan MMSE COG9 Memory	No
Popa 1994	IS	5	Meclofenoxate (MF) Antagonic Stress	DSM-III-R	AD	Mild-Mod	63	NR	69.7y (65-87y) 52%M	260 mg tid	3m	SAS-G SCAG WAIS WMS	No
Schneider 1994	NR	5	Nicergoline Antagonic Stress	DSM IV ICD-10	AD	Mild-Mod	62	NR	69.8y (65-85y) 53%M	60 mg/d	3m	SAS-G SCAG WAIS WMS	No
Xu 1999	IS	7	Huperzine capsules Huperzine tablets	NINCDS DSM-III-R	AD	Mild-Sev	60	60	72.0y (54-80y) 43%M Asian	400 µg/d	60d	CGI CGI-C GBS-SDS HDS-R IADL Memory Quotient MMSE TESS	No

EvTable84. Study results: Eptastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 29d	
Canal 1996	OC Population 1] Placebo change from baseline 2] Eptastigmine 20 mg BID or TID change from baseline 3] Difference between Placebo and Eptastigmine in change from baseline	ADL IADL LMT SWFT TMT CGI CGIC Physician CGIC Caregiver					1] 0.35 (0.32)* 2] -0.10 (0.10)* 1] 0.65 (0.40)* 2] -0.39 (0.20)* 1] 0.00 (0.65)* 2] 1.46 (0.43)* 1] -0.75 (0.54)* 2] 0.65 (0.43)* 1] -4.60 (5.13)* 2] -17.15(4.68)* 1] 0.05 (0.05)* 2] -0.14 (0.05)* 1] 4.10 (0.07)* 2] 3.68 (0.06)* 1] 3.75 (0.10)* 2] 3.54 (0.08)*	3] 0.383 3] 0.020 3] 0.157 3] 0.087 3] 0.247 3] 0.258 3] 0.006 3] 0.180

*SEM

EvTable85. Study results: Eptastigmine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 24 w	
Imbimbo 1999	ITT Population 1] Placebo 2] Eptastigmine 15 mg TID 3] Eptastigmine 20 mg TID 4] Placebo change from baseline 5] Eptastigmine 15 mg TID change from baseline 6] Eptastigmine 20 mg TID change from baseline 7] Eptastigmine 15 mg TID change from placebo 8] Eptastigmine 20 mg TID change from placebo	<u>ADAS-Cog</u> <u>CIBIC+</u> IADL					4] 2.62 (7.58) 5] 1.05 (6.79) 6] 0.41 (6.88) 4] 4.36 (0.89) 5] 4.21 (0.86) 6] 4.03 (0.33) 4] 1.23 (2.55) 5] 0.83 (2.20) 6] 0.58 (1.78)	7] 0.04 8] 0.005 7] 0.138 8] 0.001 7] 0.088 8] 0.005

EvTable86. Study results: Haboyin (Huperzine-A).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 30d**		**Final: (specify) 60d**	
XU 1999	OC Analysis 1] Haboyin (Huperzine-A) 400ug capsules bid 2] Haboyin (Huperzine-A) 400ug tablets bid 3] Capsules difference from baseline 4] Tablets difference from baseline 5] Difference between capsules and tablets	Memory Quotient	1] 40(13) 2] 43(12)	5] >0.05			1] 48(17) 2] 49(16)	3] <0.01 4] <0.01 5] >0.05
		MMSE	1] 13(5) 2] 15(4)	5] >0.05	1] 14(7) 2] 16(5)	3] <0.01 4] <0.01 5] >0.05	1] 18(8) 2] 19(6)	3] <0.01 4] <0.01 5] >0.05
		HDS-R	1] 11(5) 2] 13(5)	5] >0.05	1] 13(6) 2] 15(6)	3] <0.01 4] <0.01 5] >0.05	1] 16(8) 2] 17(7)	3] <0.01 4] <0.01 5] >0.05
		IADL	1] 21(5) 2] 22(6)	5] >0.05	1] 20(5) 2] 21(6)	3] <0.01 4] <0.01 5] >0.05	1] 19(6) 2] 19(6)	3] <0.01 4] <0.01 5] >0.05
		GBS-SDS	1] 52(23) 2] 51(21)	5] >0.05	1] 47(22) 2] 44(22)	3] <0.01 4] <0.01 5] >0.05	1] 40(25) 2] 36(24)	3] <0.01 4] <0.01 5] >0.05

EvTable87. Study results: Linopirdine.

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6m**	
Rockwood 1997 Rockwood 2000	ITT Analysis (Endpoint) 1] Placebo 2] **Linopirdine** 30 mg tid 3] **Linopirdine** vs Placebo	<u>ADAS-cog</u> <u>CGI</u> <u>CGI % improved</u> ADAS-noncog ADAS total SKT IADL Dementia behavior disturbance scale MMSE	1] 20.5 (8.44)* 2] 20.3 (8.58)* 1] 3.92 (0.87)* 2] 3.91 (0.86)*] 2.4 (2.6)* 2] 2.3 (2.6)* 1] 22.8 (9.5)* 2] 22.6 (10.0)* 1] 38.5 (6.6)* 2] 37.8 (6.3)* 1] 19.8 (5.1)* 2] 19.1 (5.2)* 1] 14.7 (9.7)* 2] 14.3 (9.6)* 1] 19.6 (4.51) 2] 19.4 (4.05)				1] 22.5 2] 20.2 1] 3.69 (0.72 2] 3.81 (0.74) 1] 13% (est) 2] 15% (est) 1] 3.4 (0.9)* 2] 3.0 (0.8)* 1] 25.4 (2.6)* 2] 23.2 (0.7)* 1] 40.8 (2.4)* 2] 39.5 (1.5)* 1] 21.2 (1.4)* 2] 20.1 (1.0)* 1] 15.7 (1.1)* 2] 14.9 (0.6)*	3] .001 3] 0.558 3] NS 3] <0.05 3] NS 3] NS 3] NS

*SEM

EvTable88. Study results: Linopirdine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 4w	
VanDyck 1997	OC Analysis 1] Placebo 2] Linopirdine 40 mg tid 3] Linopirdine vs Placebo	ADAS DBDS CGIC						3] 0.12 3] 0.13 3] 0.07

EvTable89. Study results: Sabeluzole.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 48w**	
Mohr, 1997	OC Analysis 1] Placebo 2] Sabeluzole 5 mg 3] Sabeluzole 10 mg 4] Placebo change from baseline 5] Sabeluzole 5mg change from baseline 6] Sabeluzole 10mg change from baseline 7] Between groups	ADAS-cog MMSE Cog-9 Memory	1] 20.4 (2.0)* 2] 17.8 (1.8)* 3] 23.3 (2.8)* 1] 18.5 (1.1) 2] 18.9 (0.9) 3] 17.9 (0.6) 1] 11.0 (1.8) 2] 7.2 (1.2) 3] 13.4 (2.4) 1] 10.5 (0.6) 2] 10.7 (0.7) 3] 11.5 (0.5)				1] 27.1 (2.8)* 2] 22.3 (3.0)* 3] 28.4 (3.5)* 1] 17.3 (2.9) 2] 11.3 (2.3) 3] 17.9 (2.9) 1] 11.7 (0.6) 2] 11.0 (0.8) 3] 12.2 (0.5)	4] <0.01 5] <0.05 6] <0.05 7] NS 4] <0.01 5] <0.05 6] <0.05 7] NS 4] <0.05 5] NS 6] NS 7] NS

*SEM

EvTable90. Study results: Antagonic Stress - Meclofenoxate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 3m**	
Popa, 1994	OC Population 1] Meclofenoxate (MF) 260 mg tid 2] Antagonic Stress (AS) 3] MF final v baseline 4] AS final v baseline 5] AS vs MF final	SCAG	1] 68.3 (7.2) 2] 71.2 (7.7)				1] 52.0 (7.6) 2] 46.1 (6.5)	3] <0.001 4] <0.001 5] <0.001 favors AS
		SASG	1] 67.4 (10.6) 2] 68.4 (8.9)				1] 53.3 (13.1) 2] 47.3 (6.5)	3] <0.001 4] <0.001 5] <0.01 favors AS
		WMS (MQ)	1] 82.0 (6.5) 2] 81.3 (9.8)				1] 100.0 (11.3) 2] 108.6 (11.4)	3] <0.001 4] <0.001 5] <0.05 favors AS
		WAIS (DI)	1] 13.8 (4.4) 2] 15.4 (4.3)				1] 9.8 (4.1) 2] 6.7 (3.9)	3] <0.001 4] <0.001 5] <0.010 favors AS

EvTable91. Study results: Nicergoline - Antagonic Stress.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 3m**	
Schneider 1994	OC Analysis 1] Nicergoline 20 mg tid 2] Antagonic Stress 3 capsules tid 3] Nicergoline change from baseline 4] Antagonic Stress change from baseline 5] Difference between Nicergoline and Antagonic Stress in change from baseline	SCAG SASG WAIS Digit symbol	1] 66.5 (11.5) 2] 71.2 (7.7) 1] 65.8 (9.5) 2] 68.4 (8.9) 1] 7.8 (1.2) 2] 7.5 (1.6)				1] 50.5 (8.6) 2] 46.1 (6.5) 1] 52.1 (9.4) 2] 47.3 (6.5) 1] 9.6 (1.6) 2] 11.5 (2.4)	3] <0.001 4] <0.001 5] 0.002 favors AS 3] <0.001 4] <0.001 5] 0.000 favors AS 3] <0.001 4] <0.001 5] 0.000 favors AS

EvTable92. Study results: Huperzine A.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify)		Final] (specify) 8w	
Xu 1995	OC Analysis							
	1] Placebo	MQ	1] 48 (21) 2] 56 (21)	3] >0.05			1] 52 (26) 2] 64 (26)	3]<0.05 4] <0.01 5] <0.01
	2] Huperzine A							
	3] Difference between Placebo and Huperzine A	MMS	1] 14 (5) 2] 16 (5)	3] >0.05			1] 15 (6) 2] 19 (6)	3] <0.01 4] >0.05 5] <0.01
		HDS	1] 16 (5) 2] 16 (6)	3] >0.05			1] 15 (7) 2] 20 (6)	3] <0.01 4] >0.05 5] <0.01
	4] Placebo difference from baseline							
	5] Huperzine A difference from baseline	ADL	1] 31 (9) 2] 33 (10)	3] >0.05			1] 31.9 (0.7) 2] 29 (9)	3] >0.05 4] >0.05 5] <0.01

EvTable93. Adverse Events: Neurotransmitters - Various Cholinergic neurotransmitter modifying agents.

Adverse events (AE) identified in included studies	**EPTASTIGMINE** Canal, 1996	**EPTASTIGMINE** Imbimbo, 1999	**HUPERZINE** Xu, 1995	**HUPERZINE** Xu, 1999	**LINOPIRDINE** Van Dyck, 1997	**LINOPIRDINE** Rockwood, 1997	**SABELUZOLE** Mohr, 1997	**MECLOFENOXATE ANTAGONIC STRESS** Popa, 1994	**NICERGOLINE ANTAGONIC STRESS** Schneider, 1994	**HUPERZINE** Xu, 1999
Withdrawn (%) due to AE	T: 4 C: 0	T: 8 C: 7	T: 0 C: 0	T: 0 C: 0	T: 0 C: 0	T: 21 C: 2	T: 0 C: 0	T: NR C: NR	T: NR C: NR	T: NR C: NR
AE Checklist (Max 5)	4	4	3	5	0	3	0	1	0	5
None Reported					x		x	X	X	
Balance				NS						NS
Accidental Injury										
Dizziness			NS							
Falls		x								
Behavioral			NS							
Agitation			NS	NS						NS
Cardiovascular		x								
Arrhythmia	x	x								
Hypotension										
Hypertension		x								
Extrapyramidal										
Tremor										
Gastrointestinal		x								
Abdominal pain		x								
Constipation										
Diarrhea		x	NS							
Dyspepsia										
Nausea, vomiting	x	x	NS	NS						NS
Metabolic/nutritional										
Eating disorder		x	NS	NS						NS
Weight Change										
Neurological										
Asthenia										
Psychiatric										
Anxiety		x								
Confusion, delirium		x								
Depression		x								
Respiratory		x								
Cough, cold, infection										
Rhinitis			NS							
Other		x		NS						NS
Aberrant hematology		x								
Fatigue, weakness										
Fever, flu, pneumonia		x								
Headache		x								
Hepatic abnormality						S				
Muscle/joint disorder		x								
Pain		x								
Rash, skin disorder		x								
Sleep disorder		x	NS	NS						NS
Urinary disorder		x								

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable94. Key characteristics: Haloperidol.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Allain 2000	NR	6	Placebo Tiapride Haloperidol	DSM-III-R	AD	Mild-Mod	306	259	79.6y (55-94y) 36%M	300 mg/d 6 mg/d	21d	CGI Global Improvement MMSE MOSES UKU	No
Auchus 1997	NI	6	Placebo Haloperidol Fluoxetine	NINCDS	AD	Probable	15	12	75.6y (NR) 33%M 100% Community	3 mg/d 20 mg/d	6w	BEHAVE-AD CMAI CSI	No
DeDeyn 1999	PI	7	Placebo Risperidone Haloperidol	DSM IV	PDD VaD Mixed	Severe	344	223	81.0y (median) (56-97y) 44%M 99.9% white 100% Institution	0.25 mg with increments of 0.25 every 4d then: 4 mg/d 4 mg/d	12w	BEHAVE-AD CGI CMAI CMH ECG EPS ESRS FAST Heart Rate Laboratory tests MMSE	VaD vs all

EvTable94. Key characteristics: Haloperidol cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Petrie 1982	PI	6	Placebo Loxapine Haloperidol	DSM III	PDD MID	Mod–Sev	64	37	72.7y (60-95y) 49%M 100% institution	Gradually increased with a fixed-flexible dosage for 4 w 50 mg/d 10 mg/d variable	10w	BPRS CGI CGIC EKG Laboratory tests NOSIE SCAG	No
Teri 2000	NI IS	6	Placebo Haloperidol Trazodone BMT	NINCDS	AD	Probable – Possible	149	91	74.8y (NR) 45%M 86% white	3 mg/d 300 mg/d	16w	ABID ADCS-CGIC BRSD-CERAD Caregiver Burden Screen CMAI IADL MMSE PSM RMBPC SCB	No

EvTable94. Key characteristics: Haloperidol cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
DRUG VS DRUG (NO PLACEBO)													
Carlyle 1993	NR	5	Loxapine Haloperidol	DSM-III-R	PDD AD MID	Mod-Sev	40	31	79.0y (65-91y) 55%M 100% Institution	50 mg tid 10 mg tid	28d	Aggression Chart Blood count Electrolytes ESR Renal & Liver Function Test	No
Coccaro 1990	NI IS	6	Haloperidol Oxazepam Diphenhydramine	DSM III	Dementia	NR	59	52	75.3y (58-99y) 59%M 100% Institution	Started with 0.5 or 1.0 mg/d (haloperidol), 10 or 20mg/d (oxazepam), 25 or 50 mg/d (diphenhydramine) and increased to max doses of 5 mg/d 60 mg/d 200 mg/d respectively	8w	ADAS BPRS CDRS NOSIE PSMS Treatment emergent	No
Chan 2001	NI	6	Haloperidol Risperidone	DSM IV	AD VaD	Severe	58	55	80.5y (≥55y) 28%M 100% Asian	2 mg/d	12w	BEHAVE-AD CMAI CMMSE FAST Simpson-Angus Scale	No

EvTable95. Study results: Haloperidol - Tiapride.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 21 d	
Allain 2000	ITT Endpoint Analysis 1] Placebo 2] Tiapride 100-300 mg/d 3] Haloperidol 2-6 mg/d 4] Across treatment 5] Tiapride vs Placebo 6] Haloperidol vs Placebo 7] Tiapride vs Haloperidol 8] Placebo vs Tiapride change from baseline 9] Placebo vs Haloperidol change from baseline 10] Triapride vs Haloperidol change from baseline	MOSES % responders (% with 25% decrease in irritability/ aggressiveness subscore) MOSES Global Improvement very improved Global Improvement no change CGI MMSE	1] 20.28 (2.85) 2] 19.90 (2.92) 3] 20.52 (3.27)				1] 49% 2] 63% 3] 69% 1] 15.53 (5.25) 2] 13.33 (4.20) 3] 13.75 (4.59) 1] 14% 2] 24% 3] 31% 1] 21% 2] 12% 3] 12%	8] 0.04 9] 0.004 10] 0.38 5] 0.0009 6] 0.008 7] 0.53 4] NS 8] 0.03 9] 0.02 10] NS 8] NS 9] NS 10] NS

EvTable96. Study results: Haloperidol - Fluoxetine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify)		Final] (specify) 6 w	
Auchus 1996	OC Population 1] Placebo 2] Fluoxetine 20 mg/d 3] Haloperidol 3mg/d 4] Across group treatment effect	<u>CMAI</u> BEHAVE-AD CSI	1] 34.4 (8.2) 2] 33.8 (3.0) 3] 37.4 (4.4) 1] 5.6 (3.4) 2] 7.0 (4.2) 3] 11.8 (4.9) 1] 116.2 (57.0) 2]160.4(121.8) 3] 165.4 (50.3)				1] 33.0 (3.5) 2] 35.2 (10.3) 3] 35.0 (11.2) 1] 6.6 (3.5) 2] 8.8 (3.5) 3] 9.2 (7.1) 1] 134.8 (62.1) 2] 143.6 (79.3) 3] 179.4 (91.9)	4] 0.82 4] 0.35 4] 0.67

EvTable97. Study results: Risperidone - Haloperidol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
DeDeyn 1999	ITT Population 1] Placebo 2] Haloperidol 1.2mg/d 3] Risperidone 1.1 mg/d 4] Risperidone vs Placebo 5] Risperidone vs Placebo change from baseline 6] Haloperidol vs Placebo change from baseline 7] Risperidone vs Placebo change from baseline	BEHAVE-AD total Behave-AD Aggressiveness CMAI total aggressive CMAI physical aggressive CMAI verbal aggressive CGI MMSE FAST Behave-AD % with > 30% reduction from baseline	1] 16.6 2] 16.5 3] 16.3 1] 5.0 2] 4.7 3] 5.0 1] 27.5 2] 26.3 3] 25.6 1] 19.7 2] 19.3 3] 18.9 1] 7.7 2] 7.0 3] 6.8				1] -4.2 2] -6.6 3] -5.2 1] -0.8 2] -1.6 3] -1.7 1] -1.6 2] -3.3 3] -3.9 1] -0.7 2] -0.3 3] -2.7 1] -0.8 2] -1.0 3] -1.2 1] 47% 2] 63% 3] 54%	4] 0.19 6] 0.01 4] 0.004 6] 0.01 7] 0.05 favors Risperidone 4] 0.01 7] 0.02 4] 0.01 7] 0.01 4] 0.01 5] <0.05 5] NS 5] NS 5] 0.25

EvTable98. Study results: Loxapine - Haloperidol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: 10w**	
Petrie, 1982	Efficacy Analysis Population 1] Placebo 2] Haloperidol 10 mg/d (max) 3] Loxapine 50 mg/d (max) 4] Haloperidol vs baseline 5] Loxapine vs baseline 6] Placebo vs Haloperidol change from baseline 7] Placebo vs Loxapine change from baseline	CGIC (marked or moderate improvement) BPRS total SCAG total NOSIE	 1] 46.36 2] 46.35 3] 50.79 1] 61.0 2] 55.9 3] 62.9 1] 157.2 2] 184.0 3] 155.0				1] 9% 2] 35% 3] 32% 1] 48.90 2] 39.60 3] 43.84 1] 60.9 2] 47.3 3] 54.4 1] 151.2 2] 192.0 3] 171.4	 4] < 0.05 5] < 0.05 6] <0.05 7] <0.05 4] < 0.05 5] < 0.05 5] < 0.05

EvTable99. Study results: Haloperidol - Trazodone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 16w	
Teri, 2000	Efficacy Analysis 1] BMT 2] Haloperidol mean dose1.8 mg/d 3] Trazodone mean dose 200 mg/d 4] Placebo 5] Group Effect 6] Placebo vs Trazodone 7] Placebo vs Haloperidol 8] Placebo vs BMT 9] Traxodon vs Haloperidol 10] Trazodone vs BMT 11] Haloperidol vs BMT	ADCS-CGIC %improvement BRSD Change score MMSE Change score Lawton-Brody ADL Physical Change score Lawton-Brody ADL Instrumental Change score					1] 32% 2] 32% 3] 41% 4] 31% 1] –3.56 12.85) 2] –5.35(22.41) 3] –6.95(20.87) 4] -5.28 (24.36) 1] –0.05 (2.58) 2] –0.61 (2.69) 3] –1.97 (3.15) 4] –0.28 (3.35) 1] –0.27 (1.96) 2] 2.53 (4.00) 3] 1.62 (2.56) 4] 1.31 (2.47) 1] 0.17 (1.84) 2] 1.79 (3.20) 3] 1.81 (3.32) 4] 0.89 (3.32)	6] 0.99 7] 0.81 8] 0.65 9] 0.75 10] 0.52 11] 0.86 5] NS 6] NS 7] NS 8] NS 9] NS 10] <0.05 favours BMT 11] NS 6] <0.05 favours placebo 7] <0.05 favours placebo 6] <0.05 7] <0.05 favours placebo

EvTable 99. Study results: Haloperidol - Trazodone cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		**Mid-Point: (specify)**		**Final: (specify) 16w**	
			SCB Subjective Screen for Caregiver Burden Subjective Objective					1] -2.95 (7.29 2] -1.88 (8.89) 3] -1.97 (10.06) 4] -2.58 (9.67) 1] -2.95 (7.29 2] -1.88 (8.89) 3] -1.97 (10.06) 4] -2.58 (9.67) 1] -1.23 (3.32) 2] -0.44 (3.22) 3] -1.14 (4.04) 4] -1.25 (4.02)	5] NS

EvTable100. Study results: Loxapine - Haloperidol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 14d**		**Final: (specify) 28d**	
Carlyle 1993	OC Analysis 1] Haloperidol 7.0 mg/d (mean) 2] Loxapine 36.0 mg/d (mean) 3] Difference between Haloperidol and Loxapine	Mean Aggression Score for responders Mean depression score Response rate	1] 6.0 2] 8.6		1] 4.8 2] 6.6	3] NS	1] 2.5 2] 4.2 1] 11/14 2] 14/17	3] NS 3] NS

EvTable101. Study results: Haloperidol – Oxazepam - Diphenhydramine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point:**		**Final: 8w**	
Coccaro 1990	Completers Analysis 1] Haloperidol 5 mg/d (max) 2] Oxazepam 60 mg/d (max) 3] Diphenhydramine 200 mg/d (max) 4] Between groups, change from baseline 5] Change from baseline 6] Between groups at timepoint	CDRS mean score ADAS BPRS PSMS NOSIE	1] 2.78 2] 2.76 3] 2.66 1] 11.00 (5.95) 2] 11.50 (4.90) 3] 9.82 (3.68) 1] 6.33 (3.01) 2] 5.81 (2.17) 3] 5.67 (2.72) 1] 42.17 (12.95) 2] 45.75 (11.02) 3] 39.35 (10.36) 1] 78.19 (7.67) 2] 80.69 (9.10) 3] 73.47 (5.88)	4] > 0.10			1] 8.39 (6.09) 2] 9.12 (4.33) 3] 6.12 (4.78) 1] 4.78 (2.44) 2] 5.50 (2.71) 3] 4.47 (2.85) 1] 37.89 (15.36) 2] 43.68 (11.47) 3] 34.76 (9.94) 1] 78.31 (9.45) 2] 80.69 (9.89) 3] 73.00 (11.53)	4] NS 5] < 0.001 6] NS 4] NS 5] < 0.02 6] NS 4] NS 5] < 0.001 6] NS 4] NS 5] NS 6] <0.02

EvTable102. Study results: Haloperidol - Risperidone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12 w	
Chan 2001	OC Analysis 1] Haloperidol 0.5-2 mg/d 2] Risperidone 0.5-2 mg/d 3] Haloperidol change from baseline 4] Risperidone change from baseline 5] Between treatments	CMAI BEHAVE-AD (Aggressive-ness) FAST CMMSE	1] 46.4 (10.5) 2] 48.9 (14.5) 1] 2.1 (2.0) 2] 2.2 (2.5) 1] 8.2 (5.0) 2] 7.9 (6.0)				1] 36.3 (10.4) 2] 40.8 (16.9) 1] 0.8 (1.5) 2] 0.9 (2.0) No data extracted 3] –0.15 4] –0.42	3] 0.000 4] 0.002 5] 0.95 3] 0.011 4] 0.019 5] 0.56 3] 0.84 4] 0.70

EvTable103. Adverse Events: Haloperidol.

Adverse events (AE) identified in included studies	TIAPRIDE (T1) HALOPERIDOL (T2) PLACEBO (C) Allain, 2000	HALOPERIDOL(T1) FLUOXETINE (T2) PLACEBO (C) Auchus, 1997	HALOPERIDOL (T1) RISPERIDONE (T2) PLACEBO (C) De Deyn, 1999	HALOPERIDOL (T) LOXAPINE (T2) PLACEBO (C) Petrie, 1982	HALOPERIDOL (T1) TRAZODONE (T2) PLACEBO (C) Teri, 2000
Withdrawn (%) due to AE	T1: 5 T2: 17 C: 6	T1: 33 T2: 0 C: 17	T1: NR T2: NR C: NR	T1: 18 T2: 21 C: 5	T1: NR T2: NR C: NR
AE Checklist (Max 5)	3	3	1	5	2
None Reported					
Balance		x			S*
Accidental Injury			NS*		
Dizziness					NS*
Falls			NS*		
Behavioral	x			NS*	
Agitation			NS*		
Cardiovascular	x			x	
Arrhythmia					
Hypotension	x			x	
Hypertension	x				
Extrapyramidal	S*			x	S*
Tremor	x	x			NS*
Gastrointestinal				x	
Abdominal pain					
Constipation	x				
Diarrhea	x				
Dyspepsia					
Nausea, vomiting	x				
Metabolic/nutritional					
Eating disorder					
Weight Change					
Neurological				x	
Asthenia	x				
Psychiatric					
Anxiety	x	x			
Confusion, delirium		x			
Depression		x			
Respiratory					
Cough, cold, infection					
Rhinitis					
Other	NS*			S*	NS*
Aberrant hematology					
Fatigue, weakness					NS*
Fever, flu, pneumonia					
Headache					
Hepatic abnormality					
Muscle/joint disorder					
Pain					
Rash, skin disorder					
Sleep disorder	x		NS*		
Urinary disorder	x				

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable103. Adverse Events: Haloperidol (Drug vs Drug Trials) cont'd

Adverse events (AE) identified in included studies	HALOPERIDOL (T) RISPERIDONE (C) Chan, 2001	HALOPERIDOL(T) LOXAPINE (C) Carlyle, 1993	DIPHENHYDRAMINE (T1) HALOPERIDOL (T2) OXAZEPAM (T3) Coccaro, 1990
Withdrawn (%) due to AE	T: 4 C: 7	T: 20 C: 15	T1: 5 T2: 10 T3: 11
AE Checklist (Max 5)	1	5	3
None Reported			
Balance			
Accidental Injury			
Dizziness			
Falls			
Behavioral			
Agitation		x	
Cardiovascular			
Arrhythmia			
Hypotension	NS*	x	
Hypertension			
Extrapyramidal	S*	x	x
Tremor			
Gastrointestinal			
Abdominal pain			
Constipation	x		
Diarrhea			
Dyspepsia			
Nausea, vomiting	x		
Metabolic/nutritional			
Eating disorder			
Weight Change			
Neurological			
Asthenia			
Psychiatric			
Anxiety			
Confusion, delirium		x	
Depression			
Respiratory			
Cough, cold, infection			
Rhinitis			
Other		x	x
Aberrant hematology			
Fatigue, weakness			
Fever, flu, pneumonia			
Headache			
Hepatic abnormality			
Muscle/joint disorder			
Pain			
Rash, skin disorder			
Sleep disorder	x		
Urinary disorder			

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable104. Key characteristics: Memantine.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Orgogozo 2002	IF	6	Placebo Memantine	NINDS-AIREN	VaD	Mild-Mod	321	234	76.4y (NR) 53%M 100% white	5 mg/d on w 1 10 mg/d on w 2 15 mg/d on w 3 then 20 mg/d	28w	ADAS-cog CGIC CIBIC-plus ECG GBC GBS MIS MMSE NOSGER Laboratory Tests	No
Wilcock 2002	IS	7	Placebo Memantine	DSM-III-R NINDS-AIREN	VaD	Mild-Mod	579	464	77.4y (54-97y) 51%M 100% Community	5 mg/d increasing of 5 mg/d each week for 4 w then 20 mg/d	28w	ADAS-Cog CIBIC+ CGI-C CGI-S GBS MMSE NOSGER	MMSE Type of VaD Gender
Winblad 1999	NR	6	Placebo Memantine	DSM-III-R	DAT VaD PDD	Modly Sev-Severe	166	151	71.2y (60-80y) 42%M 100% Institution	5 mg/d on w 1 then 10 mg/d	12w	BGP CGI-C CGI-S CT Scan Ferm's D-test GDS HAM-D HIS MMSE	AD/VaD Care Dependence

EvTable105. Study results: Memantine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 28w**	
Orgogozo 2002	ITT/OC Analysis 1] Placebo change from baseline 2] Memantine 20mg/d change from baseline 3] Memantine vs Placebo ITT for Primary outcomes Per protocol For Secondary outcomes	ADAS-Cog CIBIC-plus MMSE CGI-C Clinician CGI-C Caregiver NOSGER GBS					1] 1.58 (6.42) 2] –1.25 (1.39) 1] 4.11 (1.48) 2] 3.82 (1.39) 1] 0.52 (4.07) 2] 1.75 (3.38) 1] 3.85 (1.19) 2] 3.58 (1.09) 1] 3.82 (1.31) 2] 3.52 (1.26) 1] 3.26 (12.95) 2] 2.73 (11.67) 1] 3.38 (16.34) 2] –0.36(15.38)	3] 0.0016 3] 0.284 3] 0.0121 3] 0.0938 3] 0.0921 3] 0.8119 3] 0.1194

EvTable106. Study results: Memantine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 28w	
Wilcock 2002	ITT and PP Analysis 1] Placebo 2] Memantine 20mg/d 3] Placebo change from baseline 4] Memantine change from baseline 5] Memantine vs Placebo	ADAS-Cog CGI-C MMSE NOSGER GBS	 1] 67.69 (14.21) 2] 68.90 (15.84) 1] 32.15 (14.58) 2] 33.83 (14.26)				3] –2.28 (7.77) 4] –0.53 (7.02) 3] 0.51 (3.9) 4] 0.24 (3.8) 3] 3.45 (11.08) 4] 2.32 (11.12) 3] 2.48 (15.95) 4] 1.65 (12.00)	5] 0.0005 5] 0.292 5] NS 5] 0.22 5] 0.02

EvTable107. Study results: Memantine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 2h**		**Final: (specify) 24h**	
Winblad 1999	ITT Analysis 1] Placebo change from baseline 2] Memantine 10mg/d change from baseline 3] Difference between placebo and memantine in change from baseline	<u>CGI-C</u> <u>BGP</u> (care dependence) CGI-S BGP (total)			1] 40% 2] 48%		1] 46% 2] 73% 1] –1.1 (11.8) 2] –3.1 (12.2) 1] 53% 2] 78% 1] -4.6 (7.0) 2] -7.2 (7.1)	3] <0.001 3] 0.016 3] 0.015

EvTable108. Adverse Events: Memantine.

Adverse events (AE) identified in included studies	Orgogozo, 2002	Wilcock, 2002	Winblad, 1999
Withdrawn (%) due to AE	T: 12 C: 13	T: 9 C: 7	T: NR C: NR
AE Checklist (Max 5)	4	4	3
None Reported			
Balance			
Accidental Injury		x	
Dizziness	NS	x	
Falls		x	
Behavioral			
Agitation	NS	x	
Cardiovascular	NS		x
Arrhythmia			
Hypotension			
Hypertension			
Extrapyramidal		x	
Tremor			
Gastrointestinal			
Abdominal pain			x
Constipation		x	
Diarrhea		x	
Dyspepsia			
Nausea, vomiting		x	x
Metabolic/nutritional			x
Eating disorder			
Weight Change			
Neurological	NS	x	
Asthenia			
Psychiatric		x	
Anxiety			
Confusion, delirium	NS	x	
Depression			
Respiratory		x	x
Cough, cold, infection		x	
Rhinitis			
Other		x	x
Aberrant hematology			
Fatigue, weakness			
Fever, flu, pneumonia			x
Headache		x	
Hepatic abnormality			
Muscle/joint disorder		x	x
Pain		x	
Rash, skin disorder			
Sleep disorder		x	
Urinary disorder		x	

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable109. Key characteristics: Selegiline.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	#Completing Trial	Mean age (range) % Male (M)	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Agnoli 1991	NR	5	Placebo L-Deprenyl	NINCDS	PDD	Probable Mild-Mod	10	10	68.6y (NR) 40%M	5 mg bid	60d	Cerebral Blood Flow GBS RMT SPECT-Tc-HMPAO TP	No
Burke 1993a Auxiliary: Burke 1993b	PI IS	6	Placebo L-Deprenyl	NINCDS	DAT	Mild	39	33	73.1y (NR) 74%M	5 mg bid	15m	BDS BNT BPRS CDR-SB COWA CS DDS DSCS GERRI MMSE Neuropsychological Battery WAIS-R Block design WAIS-R Digit Span WSM-R	No
Filip 1998	NR	6	Placebo Selegiline (L-Deprenyl)	DSM III	PDD AD	Mild-Mod	173	142	83.0y (≥60y) 29%M 100% Institution	10 mg/d	24w	CGI Clock Drawing Test ECG EEG MMSE NOSIE Sternberg's Memory Scanning	Clock drawing test result

EvTable109. Key characteristics: Selegiline cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M)	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Freedman 1998	IS NI	5	Placebo Deprenyl	NINCDS	AD	Probable	51	41	70.4y (50-80y) 47%M	5 mg/d for 7 d then 10 mg/d	6m	ADAS-Noncog BPRS BSRT GDS COWATT MCPT CSDD MMSE RAGS-E	No
Mangoni 1991 Auxiliary: Smirne 1993	NR	7	Placebo L-Deprenyl	NINCDS DSM III	DAT PDD	Probable Mild-Mod	119	112	68.8y (NR) 38%M	10 mg/d	3m	Blessed-D Digit Span Drawing test IPSC-E Short Story TP Word Fluency WMS	GDS result
Sano 1997 Auxiliary: Thal 1996	NI IS	5	Placebo Vitamin E Selegiline Selegiline + VitaminE	NINCDS	AD	Moderate	341	341	73.4y (NR) 35%M	Vitamin E 1000 IU bid Selegiline 5mg bid	2y	ADAS-Cog Blessed Dementia Scale CDR MMSE Time to end-point (event free survival)	No

EvTable110. Study results: **Selegiline.**

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 60d**	
Agnoli 1992	OC Analysis 1] Placebo 2] L-Deprenyl 3] Difference between placebo and L-Deprenyl	RMT A&R	1] 62 (17.2) 2] 54.8 (8.6)	3] <0.05			1] 54 (16.1) 2] 64.2 (15)	3] <0.05
		RMT DR	1] 45.8 (7.3) 2] 36.6 (7.2)	3] NS			1] 40.8 (5.4) 2] 47.2 (8.0)	3] NS
		RMT MI	1] 47 (13.7) 2] 37.2 (6.1)	3] <0.05			1] 39 (12.7) 2] 49 (12.8)	3] <0.05
		TP time	1] 6.7 (2.7) 2] 6.2 (2.6)	3] <0.05			1] 7.9 (1.5) 2] 5.4 (2.7)	3] <0.05
		TP omissions	1] 11.8 (6.7) 2] 8.5 (3.9)	3] <0.05			1] 14 (6.8) 2] 5.2 (2.7)	3] <0.05
		TP errors	1] 10.4 (7.0) 2] 10.2 (14)				1] 5.8 (4.9) 2] 1.0 (1.4)	3] <0.05
		GBS Intellectual function	1] 22.4 (8.4) 2] 20 (8.9)	3] <0.05			1] 23 (11.1) 2] 18 (9.6)	3] <0.05
		GBS verb fluency	1] 8.6 (3.5) 2] 5.5 (2.5)	3] <0.05			1] 6.9 (2.5) 2] 7.1 (3.2)	3] <0.05
		GBS picture copying	1] 16 (2.9) 2] 16.2 (3)	3] <0.05			1] 13 (4.2) 2] 17.2 (3)	3] <0.05

EvTable111. Study results: Selegeline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 8m**		**Final: (specify) 15m**	
Burke 1993a Burke 1993	OC Analysis 1] Placebo 2] L-Deprenyl 3] Placebo vs. L-Deprenyl vs. baseline	CDR CDRS-sum of boxes MMSE BDS GERRI DSS DSCS CS BPRS	1] 1.0 (0.0) 2] 1.0 (0.0) 1] 5.7 (1.1) 2] 6.2 (1.4) 1] 19.6 (4.5) 2] 18.8 (5.0) 1] 5.4 (2.5) 2] 7.7 (4.0) 1] 101.2 (21.4) 2] 110.0 (30.4) 1] 1.8 (1.4) 2] 0.8 (1.0) 1] 2.1 (1.5) 2] 2.5 (1.6) 1] 4.3 (4.0) 2] 3.2 (2.3) 1] 24.4 (2.9) 2] 25.6 (3.5)		1] 1.2 (0.5) 2] 1.3 (0.5) 1] 6.7 (2.3) 2] 7.4 (2.4) 1] 17.7 (7.8) 2] 16.1 (6.2) 1] 6.1 (3.9) 2] 7.5 (4.2) 1] 106.9 (23.6) 2] 112.1 (30.7) 1] 1.5 (1.7) 2] 0.7 (1.1) 1] 2.8 (2.0) 2] 2.6 (1.9) 1] 3.2 (3.1) 2] 3.7 (3.9) 1] 24.6 (3.7) 2] 28.4 (9.0)	3] <0.01 3] <0.01 3] <0.01 3] NS 3] NS 3] NS 3] NS 3] NS 3] NS	1] 1.3 (0.5) 2] 1.3 (0.6) 1] 8.3 (3.2) 2] 7.8 (3.1) 1] 13.1 (7.4) 2] 15.5 (6.3) 1] 7.7 (3.9) 2] 9.6 (4.8) 1] 118 (23.6) 2] 113.9 (33.6) 1] 0.9 (1.8) 2] 0.5 (0.9) 1] 2.1 (2.4) 2] 2.4 (1.6) 1] 4.7 (4.7) 2] 2.4 (1.9) 1] 28.2 (6.2) 2] 25.1 (5.9)	3] 0.31 3] NS 3] 0.25 3] NS 3] NS 3] NS 3] NS 3] NS 3] NS

EvTable112. Study results: Selegiline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12w**		**Final: (specify) 24 w**	
Filip 1999	OC Analysis 1] Placebo 2] Selegiline 3] Placebo (normal subgroup by CDT) 4] Selegiline (normal subgroup by CDT) 5] Placebo (pathologic subgroup by CDT) 6] Selegiline (pathologic subgroup by CDT) 7] Selegiline vs. Placebo (ALL) 8] Selegiline vs. Placebo (normal subgroup) 9] Seleiline vs. Placebo (pathologic subgroup)	SMST-intercept SMST-slope SMST-total error CDT	1] 87.8 (56.4) 2] 97.6 (54.8) 3] 98.3 (53.0) 4] 103.6(53.4) 5] 79.6 (58.3) 6] 94.7 (55.8) 1] 6.2 (13.8) 2] 2.5 (10.8) 3] 6.3 (12.8) 4] 4.2 (8.0) 5] 6.1 (14.7) 6] 1.7 (11.9) 1] 7.4 (5.7) 2] 8.3 (6.8) 3] 6.6 (3.9) 4] 5.8 (5.1) 5] 8.0 (6.8) 6] 9.5 (7.2) 1] 3.1 (1.4) 2] 3.2 (1.2) 3] 1.8 (0.7) 4] 2.1 (0.7) 5] 4.1 (1.0) 6] 3.7 (0.9)		1] 82.0 (56.2) 2] 67.5 (42.2) 3] 86.7 (64.7) 4] 70.4 (34.9) 5] 78.3 (49.3) 6] 66.1 (45.6) 1] 4.8 (9.3) 2] 7.4 (8.4) 3] 4.9 (12.7) 4] 9.8 (10.6) 5] 4.7 (5.7) 6] 6.2 (7.0) 1] 11.1 (8.7) 2] 9.8 (7.8) 3] 9.8 (6.4) 4] 8.2 (7.8) 5] 12.1 (10.2) 6] 105. (7.7)		1] 77.8 (54.2) 2] 69.2 (51.5) 3] 73.5 (55.7) 4] 71.8 (65.2) 5] 81.1 (53.5) 6] 68.0 (44.3) 1] 4.6 (8.3) 2] 6.9 (9.5) 3] 5.8 (10.3) 4] 9.7 (11.6) 5] 3.7 (6.4) 6] 5.6 (8.1) 1] 11.3 (10.1) 2] 9.2 (8.5) 3] 9.5 (7.1) 4] 5.9 (7.3) 5] 12.8 (11.8) 6] 10.8 (8.6) 1] 3.0 (1.3) 2] 2.8 (1.4) 3] 2.7 (1.3) 4] 1.9 (1.1) 5] 3.3 (1.3) 6] 3.3 (1.31)	8] NS 9] 0.011 8] NS 9] 0.047 8] NS 9] 0.029 8] 0.001 9] NS

EvTable112. Study results: Selegiline cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		**Mid-Point: (specify) 12w**		**Final: (specify) 24 w**	
			MMSE	1] 3.9 (1.1) 2] 3.4 (1.1) 3] 3.8 (1.1) 4] 3.5 (0.8) 5] 3.9 (1.1) 6] 3.4 (1.3)				1] 3.7 (1.4) 2] 3.9 (1.1) 3] 3.6 (1.4) 4] 4.2 (1.1) 5] 3.7 (1.3) 6] 3.8 (1.1)	7] 0.004 8] 0.041 9] NS
			CGI						7] <0.005

EvTable113. Study results: Selegiline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6m**	
Freedman 1998	ITT OC Analysis 1] Placebo 2] L-Deprenyl 3] Change from baseline placebo 4] Change from baseline L-Deprenyl 5] Difference between placebo and L-Deprenyl in change from baseline	<u>BPRS</u> MMSE GDS ADAS-Noncog CSDD BSRT RAGS-E COWAT MCPT	1] 24.0 (3.3) 2] 23.8 (3.5) 1] 18.4 (4.4) 2] 17.3 (3.7) 1] 3.9 (0.8) 2] 4.3 (0.8) 1] 3.7 (3.1) 2] 3.4 (2.3) 1] 3.3 (2.3) 2] 3.1 (1.9) 1] 24.5 (11.7) 2] 20.4 (9.4) 1] 39.3 (8.8) 2] 38.1 (7.9) 1] 28.4 (15.3) 2] 26.6 (17.2) 1] 24.6 (3.0) 2] 23.4 (4.4)				1] 25.8 (6.0) 2] 24.8 (4.0) 3] 1.79 (4.5) 4] 1.02 (2.9) 1] 18.5 (6.2) 2] 17.3 (5.1) 1] 4.0 (0.8) 2] 4.4 (0.9) 1] 4.3 (4.0) 2] 2.7 (2.3) 1] 3.2 (3.0) 2] 2.6 (1.9) 1] 23.2 (12.6) 2] 20.4 (10.5) 1] 39.0 (11.1) 2] 37.6 (9.6) 1] 28.0 (18.4) 2] 22.4 (15.8) 1] 24.6 (1.8) 2] 24.6 (2.0)	5] 0.6 5] NS 5] NS 5] NS 5] NS 5] NS 5] NS 5] NS

EvTable114. Study results: Selegeline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 60d**		**Final: (specify) 90d**	
Mangoni 1991 Smirne 1993	OC Analysis 1] Placebo 2] L-Deprenyl 10 mg/d 3] ANOVA within treatment 4] Multivariate ANOVA between treatments including all four test occasions 5] Placebo GDS=3 6] Placebo GDS=4 7] Placebo GDS=5 8] L-Deprenyl GDS=3 9] L-Deprenyl GDS=4 10] L-Deprenyl GDS=5	BDS-1 daily living BDS-II Total IPSC-E Psychic Total IPSC-E Somatic Total Digit Span WMS short story – int. WMS short story-del Word fluency Drawing test	1] 8.73 (4.34) 2] 8.76 (3.98) 1] 23.57 (8.69) 2] 23.35 (7.40) 1] 104.98 (26.10) 2] 116.32 (32.39) 1] 24.71 (9.94) 2] 24.68 (9.24) 1] 4.45 (1.35) 2] 4.19 (1.64) 1] 3.73 (3.66) 2] 2.87 (2.65) 1] 2.01 (2.77) 2] 3.10 (3.08) 1] 9.41 (5.37) 2] 8.26 (5.38) 1] 12.33 (5.98) 2] 13.76 (4.97)		1] 8.94 (4.57) 2] 7.33 (3.49) 1] 20.80 (9.17) 2] 25.52 (7.06) 1] 107.49 (27.64) 2] 101.71 (21.43) 1] 25.04 (9.75) 2] 23.08 (7.00) 1] 4.24 (1.58) 2] 4.81 (1.23) 1] 2.89 (2.68) 2] 4.60 (3.69) 1] 2.49(2.78) 2] 3.30 (3.86) 1] 7.13 (4.91) 2] 9.75 (5.71) 1] 11.73 (6.14) 2] 14.78 (4.64)		1] 9.18 (4.72) 2] 6.86 (3.43) 1] 21.24 (9.21) 2] 26.69 (6.42) 1] 113.80 (31.27) 2] 96.16 (17.81) 1] 25.37 (9.38) 2] 22.27 (7.36) 1] 3.93 (1.50) 2] 4.90 (1.33) 1] 2.33 (2.88) 2] 4.94 (3.83) 1] 1.78 (2.45) 2] 3.9 (3.49) 1] 7.35 (5.84) 2] 10.47 (5.62) 1] 11.39 (6.02) 2] 15.82 (4.23)	4] <0.01 4] <0.01 4] <0.01 4] <0.05 4] <0.01 4] <0.01 4] <0.01 4] <0.01 4] <0.05

EvTable114. Study results: Selegiline cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify) 60d		Final: (specify) 90d	
			TPAT	5] 25 (9) 6] 19 (8) 7] 11 (8) 8] 24 (8) 9] 20 (9) 10] 13 (13)		5] 25 (8) 6] 15 (11) 7] 8 (10) 8] 25 (7) 9] 24 (7) 10] 16 (13)		5] 25 (8) 6] 16 (10) 7] 8 (10) 8] 27 (5) 9] 26 (5) 10] 20 (10)	

EvTable115. Study results: Selegiline - Vitamin E.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 10m**		**Final: (specify) 20m**	
Sano 1997 Thal 1996	ITT Analysis 1] Placebo 2] Vitamin E 1000IU bid 3] Selegeline 5mg bid 4] Vitamin E 1000IU bid + Selegiline 5mg bid 5] Vitamin E 1000IU bid vs Placebo from baseline 6] Selegeline 5mg bid vs Placebo from baseline 7] Vitamin E 1000IU bid + Selegiline 5mg bid vs Placebo from baseline	<u>Event-free survival</u> Event-free survival with MMSE as covariate			1] 79% 2] 86% 3] 60% 4] 80%		1] 40% 2] 51% 3] 60% 4] 49%	5] 0.077 6] 0.087 7] 0.21 5] 0.001 6] 0.012 7] 0.049

EvTable116. Adverse Events: Selegiline.

Adverse events (AE) identified in included studies	Agnoli, 1992	Burke, 1993	Filip, 1999	Freedman, 1998	Mangoni, 1991	Sano, 1997
Withdrawn (%) due to AE	T: 0 C: 0	T: 0 C: 0	T: 9 C: 4	T: 0 C: 0	T: 4 C: 2	T: 0 C: 0
AE Checklist (Max 5)	0	3	1	3	3	1
None Reported	X	X				
Balance						S*
Accidental Injury						
Dizziness				X	X	
Falls						S*
Behavioral						
Agitation				X		
Cardiovascular			X			NS*
Arrhythmia				X		
Hypotension						
Hypertension						
Extrapyramidal						NS*
Tremor				X		
Gastrointestinal				X	X	NS*
Abdominal pain						
Constipation						
Diarrhea						
Dyspepsia					X	
Nausea, vomiting					X	
Metabolic/nutritional				X		
Eating disorder						
Weight Change				X		
Neurological			X			NS*
Asthenia						
Psychiatric			X			
Anxiety					X	
Confusion, delirium				X		
Depression						
Respiratory						
Cough, cold, infection						
Rhinitis						
Other			X	X	X	S*
Aberrant hematology						
Fatigue, weakness						
Fever, flu, pneumonia			X			
Headache				X		
Hepatic abnormality						
Muscle/joint disorder						
Pain						
Rash, skin disorder				X		NS*
Sleep disorder				X		
Urinary disorder						

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Dehlin 1985	NR	6	Placebo Alaproclate	DSM III	PDD MID Mixed	Mild-Sev	43	40	82.0y (65-93y) 44%M 100%Institution	200 mg bid	4w	CPRS GBS	No
Alvarez 2000	PI	5	Placebo Anapsos	NINCDS DSM IV	AD VaD	Mild-Mod	45	42	Mean NR (≥50y) %M NR 100% Community	360 mg/d or 720 mg/d	4w	ADAS-Cog	Disease Severity
Cutler 1993	PI	6	Placebo BMY	DSM-III-R NINCDS	AD	Mild-Mod	69	54	72.0y (54-92y) 41%M	300 mg tid	12w + 4w washout	ADAS CGI CNTB GERRI MMSE WFT	No
Tariot 1998	NI IS	7	Placebo Carbamazepine	DSM-III-R NINCDS	AD Mixed VaD	Probable	51	47	85.5y (>60y) 20%M 98% White 100%Institution	100 mg/d (start) increase by 50 mg q2-5d; modal dose: 300 mg/d	6w	BPRS BRSD CGI MMSE Overt Aggression Scale PSMS	No
Olin 2001	NI	5	Placebo Carbamazepine	NINCDS	AD	Mild-Sev	21	16	74.7y (63-86y) 33%M 71% White 100% Community Agitation	100 mg/d (Day 1-3) 100 mg bid (Day 4-7) 100 mg tid (Day 8-14) 100 mg qid (end)	6w	BPRS CBC/SMAC Levels CGIC Ham-D IADL MMSE PSMS	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Nyth 1990	NR	7	Placebo Citalopram	DSM III	AD, SDAT VaD PDD MID	Mild-Mod	98	61	77.6y (NR) 22%M	20 mg/d for 2 w 30 mg/d for 2 w	4w	CGI GBS MADRS UKU side-effect rating scale Laboratory tests	AD/SDAT vs VaD
Pollock 2002	NI	6	Placebo Citalopram Perphenazine	DSM IV NINCDS	AD VaD MIXED	Probable Possible	85	39	80.6y (NR) 35%M 90% White	10 mg/d (c) or 0.05 mg/kg (p) for 3 d 20 mg/d (c) 0.1 mg/kg/d (p) for 14 d	17d	BPRS Laboratory tests MMSE Neurobehavioural Rating Scale UKU Side effect scale	No
Porsteinsson 2001	IS PI	7	Placebo Divalproex	DSM IV NINCDS	AD VaD MIXED	Probable Possible	56	49	85.0y (>60y) 30%M 100% Institution	375 mg/d + 125 mg/q3d (until side effects)	6w	BPRS BRSD CGI CMAI MMSE Overt Aggression Scale PSM	No
Tariot 2000b	IF	6	Placebo Divalproex	DSM IV	DAT VaD	Probable Possible	173	100	83.4y (68-100y) 35%M 158 White 11 Black 3 Hispanic 100% Institution	125 mg bid + 125 mg/d until 20 mg/kg/d	6w	BPRS BRMS CGI CMAI Laboratory tests MMSE	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Olafsson 1992	NR	6	Placebo Fluvoxamine	DSM III	SDAT MID PDD	NR	46	29	81.0y (median) (65-93y) 41%M 100% Institution	50 mg/d (start) 150 mg/d (end)	6w	GBS Scale Neuropsychological Battery Trail Making Test	No
Reifler 1989	NI IS	6	Placebo Imipramine	DSM III	PDD AD	Mild-Mod	61	57	72.0y (NR) 41%M 100% Community Depression	25 mg/d + 25 mg/w until therapeutic response 83 mg/d (mean)	8w	DRS ECG Ham-D HDS MMSE OARSADL WAIS-R	Depression
Claus 1998	NR	5	Placebo Lisuride	NINCDS	AD	Mild-Modly Sev	22	22	74.1y (NR) 50%M	0.075 mg/d (start) increments of 0.075 mg/w until 0.3 mg/d	8w	CGI CVLT DMSE MMSE	No
Thal 2000b	PI	5	Placebo Lu 25-109	NINCDS	AD	Mild-Mod	496	303	75.5y (47-95y) 42%M 92% White 8% Other Community (100%)	2 weeks dose titration then fixed doses: 25, 50, or 100 mg bid	6m	ADAS-Cog ADCS-CGIC ADCS-ADL BEHAVE-AD	No
Fuchs 1992	NR	5	Placebo Maprotiline	DSM-III-R	PDD	NR	127	94	80.0y (median) (48-96y) 43%M 100% Institution Mild depression	From 25 to 75 mg tid	8w	Blood pressure GDS MMS Std Video rating of global impression	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Passeri 1987	NR	6	Placebo Minaprine	DSM III NINCDS	MID SDAT	Probable	122	122	Mean NR (60-80y) 30%M 100% Institution	100 mg bid	3m	CGI HDRS Neuropsychological Battery Nowlis MRS SHGRS SRT TP	SDAT vs MID
Roth 1996	NR	7	Placebo Moclobemide	DSM III	AD	Mild-Mod	511	NR	73.6y (60-90y) 25%M 22% Community 78% Institution, Depression	400 mg/d	6w	BGP CGAE CGI-T ECG HAM-D MMSE SCAG	No
Moller 2001	NR	7	Placebo Naftidrofuryl	NINDS-AIREN DSM-III-R	VaD MIXED	Mild-Sev	378	278	71.5y (50-85y) 45%M	600 mg/d or 600 mg/d	6m	ADAS-cog CGI CT HIS Laboratory tests MADRS MMSE MRI NOSGER SCAG Trage 8 test kit	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Street 2000 Auxiliary: Clark 2001 Kennedy 2001 Mintzer 2001 Street 2002	IF	8	Placebo Olanzapine	NINCDS	AD	Moderate	206	152	82.8y (61-97y) 39%M 100% Institution	Fixed doses: 5, 10 or 15 mg/d	6w	ADAS-Cog Barnes Akathisia BPRS ECG EPS scales MMSE NPI/NH Simpson-Angus Gait	Psychosis Cognitive impairment level
Amaducci 1988 Auxiliary: SMID 1987	IS	5	Placebo Phosphatidylserine	NINCDS	AD	Mild-Sev	142	115	62.1y (40-80y) 40%M 100% Institution	200mg/d	3m	BDS Block tapping BSR CASE RMT SCT test Self Test TK	Severity of illness
Crook 1992a	PI	5	Placebo Phosphatidylserine	NINCDS DSM III	AD PDD	Mild-Mod	51	49	71.0y (55-85y) 31%M 100% Community	100 mg tid	12w	CGI Concern of memory Facial recognition First-last name test Interviewer notices memory loss MMSE Name-Face association Recall Tests Verbal Selective Reminding WAIS	Severity of illness

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Magai 2000	PI	7	Placebo Sertraline	DSM IV NINCDS	AD	Late-stage	31	27	89.0y (NR) 0%M 84% White 16% Other 100% Institution Major depression	25 mg/d (week 1-2) 50 mg/d (week 3-4) 100 mg/d (week 5-6)	8w	AFBS CMAI CSDD Facial Behavior GS	No
Lyketsos 2000	NI	6	Placebo Sertraline	NINCDS DSM IV	AD	Mild-Mod	22	16	77.0y (NR) 41%M 77% White 23% Other 100% Community Depression	25 mg/d (start) increased by 50 mg/w to 150/d	13w	ADL CS HAM-D IADL MMSE PDRS	No
Petracca 2001	NR	7	Placebo Fluoxetine	NINCDS DSM IV	AD	Probable	41	35	70.8y (NR) 45%M 76% Major depression 24% minor depression	10 mg/d for w 1 20 mg/d for w 2 30 mg/d for w 3 40 mg/d for w 4 to 6	6w	CGI FIM HAM-A HAM-D MMSE	No
Auchus 1997	NI	6	Placebo Haloperidol Fluoxetine	NINCDS	AD	Probable	15	12	75.6y (NR) 33%M 100% Community	3 mg/d 20 mg/d	6w	BEHAVE-AD CMAI CSI	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Katz 1999 Auxiliary: Jeste 2000 Pryse-Phillips 2000	IF IS	6	Placebo Risperidone	DSM IV	AD VaD Mixed	Mod-Sev	625	435	82.7y (≥55y) 32%M 100% Institution	0.5, 1.0 or 2.0 mg/d	12w	BEHAVE-AD	Gender Age Race
Teri 2000	NI IS	6	Placebo Haloperidol Trazodone BMT	NINCDS	AD	Probable Possible	149	91	74.8y (NR) 45%M 85% White 15% Other Community	Haloperidol: 0.5 mg/d (start) 3 mg/d (end) Trazodone: 50 mg/d (start) 300 mg/d (end)	16w	ABID ADCS-CGIC BRSD-CERAD Caregiver Burden Screen CMAI IADL MMSE PSM RMBPC SCB	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
DeDeyn 1999	PI	7	Placebo Risperidone Haloperidol	DSM IV	PDD VaD Mixed	Severe	344	223	81.0y (median) (56-97y) 44%M	Titration: 0.25 mg q4d up to 1 mg bid, then if no therapeutic effect and no signs of EPS 4 mg/d 4 mg/d	12w	BEHAVE-AD CGI CMAI ECG EPS ESRS FAST Laboratory tests MMSE	No VaD vs ALL
Allain 2000	NR	6	Placebo Tiapride Haloperidol	DSM-III-R	AD	Mild-Mod	306	259	79.6y (55-94y) 36%M 100% White 100% Institution Irritability Aggressiveness	Tiapride: 100 mg/d (Day 1-3) 200 mg/d (Day 4-end) Haloperidol: 2 mg/d (Day 1-3) 4 mg/d (Day 4-end)	21d	CGI Global Improvement MMSE MOSES UKU	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Meehan 2002	IF	6	Placebo Olanzapine Lorazepam	NINCDS DSM IV	AD VaD MIXED	Possible-Probable	272	248	77.6y (54-97y) 39%M 92% White 100%Institution Agitation	Additional injections optional Olanzapine: 12.5 mg/d (max) Loxapine: 2.5 mg/d (max)	24h	ACES BPRS Positive BPRS Total CGI-S CMAI COSTART ECG MMSE Total NPI/NH PANSS-EC Simpson-Angus score	No
Barnes 1982	PI	6	Placebo Thioridazine Loxapine	DSM III	PDD MID	NR	60	34	83.0y (>65y) %M NR 100% Institution Irritability, agitation	Titration: 1 capsule every 2-5 days as needed Thioridzine: 25 mg/d (start) 62.5 mg/d (mean) Loxapine: 5 mg/d (start) 10.5 mg/d (mean)	8w	BPRS CGI NOSIE SCAG	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Pollock 2002	NI	6	Placebo Citalopram Perphenazine	DSM IV NINCDS	AD VaD MIXED	Mod-Sev	85	39	80.6y (NR) 35%M 89% White 100% Institution	Citalopram: 10 mg/d (Day 1-3) 20 mg/d (Day 4-17) Perphenazine: 0.05 mg/kg/d (Day 1-3) 0.1 mg/kg/d (Day 4-17)	17d	BPRS Laboratory tests MMSE Neurobehavioural Rating Scale UKU Side effect scale	No
Bodick 1997 Auxiliary: Veroff 1998 Satlin 1997	IF	6	Placebo Xanomeline	NINCDS	AD	Mild-Mod	343	205	75.0y (60-90y) 43%M 92% White 8% Other 100% Community	75mg/d, or 150 mg/d or 225 mg/d	6m	ADAS-Cog ADSS CIBIC+ CNTB IADL MMSE NOSGER	No
Chan 2001	NI	6	Haloperidol Risperidone	DSM IV	AD VaD	Severe	58	55	80.5y (≥55y) 28%M Community and institution All Chinese	Titration: increases of 0.5 mg/q2d 2 mg/d	12w	BEHAVE-AD CMAI CMMSE FAST Simpson-Angus Scale	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Taragano 1996	NR	7	Fluoxetine Amitriptyline	NINCDS	AD	Probable	37	25	72.1y (NR) 22%M	10 mg/d 25 mg/d	45d	HAM-D MMSE	No
Ancill 1991	IF	6	Lorazepam Alprazolam	DSM-III-R	AD	NR	40	27	78.9y (>65y) 50%M 100% Institution Agitation	0.5 mg tid 0.25 mg tid	28d	AE CGI	No
Karlsson 2000	PI	7	Citalopram Mianserin	DSM-III-R	AD	Mild-Mod	345 53 demented	289 50 demented	75.0y (64-95y) 21%M 58% Community 42% Institution Major depression	Citalopram: 20 mg/d (week 1-4) 40 mg/d (week 5-12) Mianserin: 30 mg/d (week 1-4) 60 mg/d (week 5-12)	12w	CGI GBS MADRS MMSE WHO Well-being	No
Coccaro 1990	NI IS	6	Haloperidol Oxazepam Diphen-hydramine	DSM III	PDD	Mild-Sev	59	52	75.3y (58-99y) 59%M 100% Institution Agitation	5 mg/d 60 mg/d 200 mg/d	8w	ADAS BPRS CDRS NOSIE PSMS	No
Carlyle 1993	NR	5	Loxapine Haloperidol	DSM-III-R	PDD AD MID	Mod-Sev	40	31	79.0y (65-91y) 55%M 100% Institution Aggression	Loxapine: 5 mg bid (start) 50 mg tid (end) Haloperidol: 1 mg bid (start) 10 mg tid (end)	28d	Aggression Chart Blood count Electrolytes ESR Renal & Liver Function Test	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Passeri 1993	NR	5	5'-MTHF Tradozone	DSM III-R	AD MID	Mild-Moderate	96	96	Mean NR (65-94y) 45%M Depression	50 mg/d 100 mg/d	8w	Blood levels HDRS RVM – immediate recall RVM – delayed recall	AD vs MID
Gutzmann 1997	NR	7	Tiapride Melperone	DSM-III-R	Mixed	Mild-Sev	176	156	73.8y (40-100y) 29%M 100% Institution	400 mg/d 100 mg/d	28d	AGGR AIMS BePU (German Test) Laboratory tests CGI CLEX MMSE NOSIE RAPSU (German Test) VAS-ADL	No
Katona 1998	NR	6	Paroxetine Imipramine	DSM-III-R	PDD	Mild-Mod	198	147	76.6y (59-98y) 22%M 99% White 1% Other Depression	Paroxetine: 20 mg/d (week 1-2) 30 mg/d (week 3-4) 40 mg/d (end) Imipramine: 25 mg/d (3d) 50 mg/d (11d) 75 mg/d (2w) 100 mg/d (end)	8w	CGI Cornell Rating Scale GBS MADRS	No

EvTable117. Key Characteristics. Various non-cholinergic neurotransmitter/neuropeptide modifying agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Petrie 1982	PI	6	Placebo Loxapine Haloperidol	DSM III	PDD MID	Mod–Sev	64	37	72.7y (60-95y) 49%M 100% insstitution	Gradually increased with a fixed-flexible dosage for 4 w 50 mg/d 10 mg/d variable	10w	BPRS CGI CGIC EKG Laboratory tests NOSIE SCAG	No

EvTable118. Study results: Alaproclate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Dehlin 1985	Endpoint Analysis 1] Placebo 2] Alaproclate 200 mg bid 3] Alaproclate vs. Placebo		Estimated				Estimated	
		GBS motor function	1] 13.2 2] 9.8)				1] 14.1 2] 8.9	3] <0.05
		GBS intellectual function	1] 25.7 2] 21.8				1] 26.4 2] 20.1	3] NS
		GBS emotional function	1] 6.0 2] 4.8				1] 5.3 2] 3.8	3] NS

EvTable119. Study results: Anapsos.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 4w**	
Alvarez, 2000	OC Analysis 1] Placebo total population 2] Anapsos 360 mg qid total population 3] Anapsos 720mg qid total population 4] Placebo mild dementia subpopulation 5] Anapsos 360 mg qid mild dementia sub-population 6] Anapsos 720 mg qid mild dementia subpopulation 7] Placebo Alzheimer's Disease subpopulation	ADAS-Cog	1] 28.78 (4.06)* 2] 36.07 (4.17)* 3] 34.44 (3.16)* 4] 21.00 (4.09)* 5] 27.98 (4.53)* 6] 28.15 (3.59)* 7] 29.34 (7.93)* 8] 30.56 (6.08)* 9] 39.23 (3.19)* 10] 8.47(4.92)* 11] 43.42 (4.19)* 12] 29.64 (5.04)*				1] 29.20 (3.84)* 2] 34.60 (4.48)* 3] 35.11 (3.45)* 4] 22.51 (4.04)* 5] 25.42 (4.57)* 6] 27.21 (3.60)* 7] 30.88 (8.09)* 8] 28.04 (6.48)* 9] 40.31 (3.68)* 10] 28.27 (4.32)* 11] 43.35 (4.07)* 12] 29.91(5.38)*	2] <0.05 vs. baseline 5] <0.05 vs. baseline 5] <0.01 vs. placebo 8] <0.05 vs. baseline 8] <0.05 vs. placebo

EvTable119. Study results: Anapsos cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify)		Final: (specify) 4w	
		8] Anapsos 360 mg QID Alzheimer's Disease subpopulation 9] Anapsos 720 mg QID Alzheimer's Disease subpopulation 10] Placebo Vascular Dementia subpopulation 11] Anapsos 360 mg QID Vascular Dementia subpopulation 12] Anapsos 720 mg QID Vascular Dementia subpopulation							

* SEM

EvTable120. Study results: BMY-21,502.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Cutler, 1993	OC Analysis 1] Placebo 2] BMY-21,502 300mg tid 3] BMY-21,502 vs. Placebo 4] Placebo change from baseline 5] BMY-21,502 change from baseline	MMSE ADAS CGI	1] 22.5 2] 23.5	3] >0.05 3] NS 3] >0.05			4] -0.5 5] -1.5 1] 3.69 2] 3.64	 3] NS 3] >0.05

EvTable121. Study results: Carbamazepine

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Tariot, 1998	ITT Analysis 1] Placebo 2] Carbamazepine 304 mg tid variable 3] Difference in change between Placebo and Carbamazepine	<u>CGI improved</u> <u>BPRS total</u> OAS BRS for Dementia	 1] 53.3 (8.8) 2] 55.1 (9.6) 1] 13.2 (6.3) 2] 15.0 (6.4) 1] 63.1 (25.8) 2] 77.7 (34.8)				1] 21% 2] 77% 1] 52.4 (9.8) 2] 47.4 (10.2) 1] 11.3 (7.3) 2] 8.3 (8.0) 1] 55.0 (29.2) 2] 53.4 (32.0)	 3] 0.001 3] 0.0003 3] 0.008 3] 0.03

EvTable122. Study results: Carbamazepine

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6w	
Olin, 2001	OC Population 1] Placebo change from baseline 2] Carbamazepine 400 mg/d variable change from baseline 3] Difference between Placebo and Carbamazepine change from baseline	<u>BPRS total</u> <u>CGIC % improved or no change</u> Ham-D PSMRS IADL MMSE					1] -4.2 (8.2) 2] -4.0 (7.9) 1] 58% 2] 89% 1] -1.4 (3.3) 2] -4.2 (4.3) 1] -0.6 (1.6) 2] -0.5 (1.6) 1] 0.3 (2.2) 2] 0.7 (2.2) 1] -0.5 (2.9) 2] -0.1 (2.7)	3] 0.519 3] 0.055 3] 0.150 3] 1.00 3] 0.408 3] 0.644

EvTable123 Study results: Citalopram.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 4w**	
Nyth, 1990	OC Analysis 1] Placebo average rating scores AD/SDAT 2] Citalopram 30 mg/d variable average rating scores AD/SDAT 3] Improvement between group differences AD/SDAT 4] Placebo vs Citalopram VaD	CGI-SI CGI-ANS GBS-MI GBS-II GBS – EB GBS-Confus. GBS-Irritabiliy GBS-anxiety GBS-restless MADRS Total score	1] 3.909 2] 3.897 1] 1.795 2] 1.607 1] 7.813 2] 6.667 1] 20.063 2] 22.666 1] 4.406 2] 4.555 1] 1.188 2] 1.223 1] 0.969 2] 1.297 1] 0.876 2] 1.408 1] 0.782 2] 0.888 1] 7.690 2] 8.307				1] 4.032 2] 3.897 1] 1.971 2] 1.643 1] 7.813 2] 6.667 1] 19.875 2] 21.333 1] 3.781 2] 3.296 1] 1.063 2] 0.704 1] 0.938 2] 0.667 1] 0.688 2] 0.889 1] 0.719 2] 0.444 1] 7.690 2] 6.115	3] 0.284 4]NS 3] 0.423 4] NS 3] 0.731 4] NS 3] 0.321 4] NS 3] 0.384 4] NS 3] 0.148 4] NS 3] 0.017 4] NS 3] 0.276 4] NS 3] 0.081 4] NS 3] 0.358 4] NS

EvTable124. Study results: Citalopram.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) up to 17d	
Pollock, 2002	ITT Analysis 1] Placebo 2] Citalopram 20 mg/d 3] Perphenazine 0.1mg/kg/d 4] Citalopram vs. placebo 5] Perphenazine vs. placebo	Neuro-Behavioural Rating Score	1] 58.3 (11.9) 2] 53.5 (10.2) 3] 57.1 (14.0)				1] 56.0 (15.2) 2] 43.5 (12.1) 3] 49.9 (14.2)	4] 0.002 5] 0.14

EvTable125. Study results: Divalproex.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6w	
Porsteinsson 2001	OC Analysis 1] Placebo 2] Divalproex 826 mg/d variable 3] Difference between Placebo and Divalproex change from baseline	<u>BPRS-total</u>	1] 55.4 (7.4) 2] 543.9 (8.7)				1] 49.5 (10.5) 2] 47.9 (12.4)	3] 0.61
		Overt Aggression Scale	1] 16.9 (9.0) 2] 14.8 (7.6)				1] 12.0 (8.5) 2] 10.0 (8.3)	3] 0.95
		CERAD BRSD Weighted	1] 53.9 (20.9) 2] 48.2 (16.2)				1] 45.3 (26.0) 2] 38.3 (9.9)	3] .73
		CMAI	1] 77.2 (21.1) 2] 77.2 (18.9)				1] 69.9 (22.9) 2] 67.7 (23.3)	3] 0.65
		MMSE	1] 6.7 (6.7) 2] 7.0 (6.6)				1] 5.1 (6.2) 2] 5.2 (6.9)	3] 0.91
		PSMS	1] 14.3 (4.8) 2] 15.4 (4.4)				1] 14.6 (4.7) 2] 15.2 (4.5)	3] 0.41
		CGI % with therapeutic effect					1] 52% 2] 68%	3] 0.07

EvTable125. Study results: Divalproex.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6w	
Porsteinsson 2001	OC Analysis 1] Placebo 2] Divalproex 826 mg/d variable 3] Difference between Placebo and Divalproex change from baseline	<u>BPRS-total</u>	1] 55.4 (7.4) 2] 543.9 (8.7)				1] 49.5 (10.5) 2] 47.9 (12.4)	3] 0.61
		Overt Aggression Scale	1] 16.9 (9.0) 2] 14.8 (7.6)				1] 12.0 (8.5) 2] 10.0 (8.3)	3] 0.95
		CERAD BRSD Weighted	1] 53.9 (20.9) 2] 48.2 (16.2)				1] 45.3 (26.0) 2] 38.3 (9.9)	3] .73
		CMAI	1] 77.2 (21.1) 2] 77.2 (18.9)				1] 69.9 (22.9) 2] 67.7 (23.3)	3] 0.65
		MMSE	1] 6.7 (6.7) 2] 7.0 (6.6)				1] 5.1 (6.2) 2] 5.2 (6.9)	3] 0.91
		PSMS	1] 14.3 (4.8) 2] 15.4 (4.4)				1] 14.6 (4.7) 2] 15.2 (4.5)	3] 0.41
		CGI % with therapeutic effect					1] 52% 2] 68%	3] 0.07

EvTable126. Study results: Divalproex.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Tariot 2001b	ITT Analysis 1] Placebo 2] Divalproex Sodium 20 mg/kg/d variable 3] Placebo change from baseline 4] Divalproex change from baseline 5] Divalproex vs. Placebo	<u>BRMS</u> CMAI Total score BPRS Total score CGI (Part II) MMSE	1] 17.7 (0.50)* 2] 17.2 (0.48)* 1] 81.8 (2.70)* 2] 86.8 (2.63)* 1] 41.7 (1.33)* 2] 43.3 (1.29)* 1] 7.7 (0.77)* 2] 7.1 (0.75)*				3] -3.9 (0.79)* 4] -3.9 (0.77)* 3] -7.3 (2.72)* 4] -14.3 (2.65)* 3] -7.1 (1.73)* 4] -8.0 (1.67)* 3] 3.4 (0.14)* 4] 3.9 (0.15)*	5] 0.941 5] 0.035 5] 0.690 5] 0.035 favors placebo 5] NS

*SEM

EvTable127. Study results: Fluvoxamine.

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Olafsson	OC Analysis 1] Placebo 2] Fluvoxamine 150 mg/d 3] Placebo difference from baseline 4] Fluvoxamine difference from baseline 5] difference between changes in Placebo and Fluvoxamine	Trail-making test - Median (range) GBS - Median (range) *Picture recall* Immediate recall Delayed recall *Picture recognition* Correct recognition Concept distracters Other distracters *Finger Tapping* Dominant index finger	1] 2.8 (0-16) 2] 8.3 (0-15) 1] 63 (22-104) 2] 78 (13-132) 1] 0.2 (0-5) 2] 0.4 (0-4) 1] 0.1 (0-2) 2] 0.2 (0-3) 1] 2.5 (0-8) 2] 3.7 (1-8) 1] 1.5 (0-7) 2] 0.8 (0-4) 1] 2.2 (0-8) 2] 1.3 (0-6) 1] 31 (12-59) 2] 20 (0-60)				1] 0.8 (0-8) 2] 5.0 (0-17) 1] 68 (17-102) 2] 68 (19-120) 1] 0.2 (0-4) 2] 0.6 (0-4) 1] 0.1 (0-4) 2] 0.4 (0-4) 1] 4.8 (0-8) 2] 4.8 (0-8) 1] 2.5 (0-7) 2] 1.0 (0-8) 1] 3.0 (0-6) 2] 1.0 (0-8) 1] 30 (5-67) 2] 14 (0-64)	3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS 3] NS 4] NS 5] NS

EvTable128. Study results: Fluxoxamine cont'd.

REF ID#	Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
			Non-dominant index finger	1] 25 (0-48) 2] 20 (0-50)				1] 31 (0-51) 2] 16 (0-54)	3] NS 4] NS 5] NS

EvTable127. Study results: Fluvoxamine.

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Olafsson	OC Analysis 1] Placebo 2] Fluvoxamine 150 mg/d 3] Placebo difference from baseline 4] Fluvoxamine difference from baseline 5] difference between changes in Placebo and Fluvoxamine	Trail-making test - Median (range)	1] 2.8 (0-16) 2] 8.3 (0-15)				1] 0.8 (0-8) 2] 5.0 (0-17)	3] NS 4] NS 5] NS
		GBS - Median (range)	1] 63 (22-104) 2] 78 (13-132)				1] 68 (17-102) 2] 68 (19-120)	3] NS 4] NS 5] NS
		Picture recall Immediate recall	1] 0.2 (0-5) 2] 0.4 (0-4)				1] 0.2 (0-4) 2] 0.6 (0-4)	3] NS 4] NS 5] NS
		Delayed recall	1] 0.1 (0-2) 2] 0.2 (0-3)				1] 0.1 (0-4) 2] 0.4 (0-4)	3] NS 4] NS 5] NS
		Picture recognition Correct recognition	1] 2.5 (0-8) 2] 3.7 (1-8)				1] 4.8 (0-8) 2] 4.8 (0-8)	3] NS 4] NS 5] NS
		Concept distracters	1] 1.5 (0-7) 2] 0.8 (0-4)				1] 2.5 (0-7) 2] 1.0 (0-8)	3] NS 4] NS 5] NS
		Other distracters	1] 2.2 (0-8) 2] 1.3 (0-6)				1] 3.0 (0-6) 2] 1.0 (0-8)	3] NS 4] NS 5] NS
		Finger Tapping Dominant index finger	1] 31 (12-59) 2] 20 (0-60)				1] 30 (5-67) 2] 14 (0-64)	3] NS 4] NS 5] NS
		Non-dominant index finger	1] 25 (0-48) 2] 20 (0-50)				1] 31 (0-51) 2] 16 (0-54)	3] NS 4] NS 5] NS

EvTable128. Study results: Imipramine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Reifler 1998	OC Analysis 1] Placebo Depressed group 2] Imaprine 83 mg/d Depressed group 3] Placebo Not Depressed Group 4] Imaprine 83mn/d Not Depressed Group 5] Imipramine vs. Placebo Depressed group 6] Imipramine vs. Placebo Not Depressed group	HDS MMSE DRS OARS-ADL	1] 18.6 (4.0) 2] 19.3 (3.5) 3] 6.8 (2.4) 4] 6.9 (2.9) 1] 18.0 (5.5) 2] 16.9 (4.6) 3] 14.8 (15.1) 4] 13.4 (6.9) 1] 115.9 (14.3) 2] 111.2 (14.3) 3] 98.6 (24.8) 4] 80.4 (44.6) 1] 19.6 (3.9) 2] 19.5 (3.6) 3] 19.5 (3.8) 4] 16.7 (5.8)				1] 10.8 (3.5) 2] 11.5 (3.7) 3] 6.5 (1.8) 4] 7.9 (3.1) 1] 19.3 (6.5) 2] 18.7 (5.4) 3] 15.1 (6.2) 4] 13.1 (7.7) 1] 117.4 (13.7) 2] 104.3 (20.9) 3] 98.1 (26.4) 4] 72.7 (43.8) 1] 17.8 (4.1) 2] 18.0 (3.8) 3] 18.3 (3.5) 4] 15.5 (5.4)	5] NS 6] NS 5] NS 6] NS 5] <0.01 6] <0.01 5] NS 6] NS

EvTable129. Study results: Lisuride.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Claus, 1998	OC Analysis 1] Placebo 2] Lisuride 0.3 mg tid 3] Placebo vs. Lisuride in change from baseline	MMSE	1] 18.7 (5.5)* 2] 22.9 (3.8)*				1] 17.1 (5.7)* 2] 22.6 (4.9)*	3] 0.03
		Dementia Mood Assessment Scale	1] 23.3 (4.5)* 2] 19.9 (3.3)*				1] 25.9 (5.2)* 2] 21.6 (3.8)*	3] 0.71
		CGI Improved					1] 8.3% 2] 20%	3] 0.72
		CVLT Total recall	1] 17.6 (2.3)* 2] 23.5 (3.1)*				1] 16.3 (2.8)* 2] 26.6 (3.2)*	3] 0.06
		Verbal Fluency Total correct	1] 12.3 (2.0) 2] 17.3 (2.5)				1] 11.2 (1.9) 2] 20.0 (3.7)	3] 0.10
		Visuospatial Associative Learning	1] 18.4 (4.4) 2] 20.1 (3.8)				1] 11.1 (3.6) 2] 14.7 (2.4)	3] 0.73
		Delayed Matching to sample	1] 12.4 (2.2) 2] 15.9 (2.5)				1] 10.8 (2.0) 2] 16.3 (2.1)	3] 0.59
		Working Memory Test between errors	1] 27.1 (9.8) 2] 49.9 (9.4)				1] 28.9 (9.8) 2] 28.6 (6.6)	3] 0.22
		Working Memory Test within errors	1] 2.1 (0.8) 2] 3.1 (1.2)				1] 1.8 (0.8) 2] 1.6 (0.4)	3] 0.46
		Visual Vigilance Task	1] 18.7 (5.1) 2] 18.7 (2.9)				1] 22.5 (5.5) 2] 11.7 (3.1)	3] 0.09
		Pegboard	1] 104.3 (24.4) 2] 139.7 (8.1)				1] 118.3 (14.9) 2] 136.1 (14.4)	3] 0.28

EvTable130. Study results: Lu25-109.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 24w	
Thal, 2000b	ITT Analysis 1] Placebo change from baseline 2] Lu25-109 25 mg tid change from baseline 3] Lu25-109 50 mg tid change from baseline 4] Lu25-109 100 mg tid change from baseline 5] General linear ANCOVA vs. baseline	<u>ADAS-Cog</u> <u>ADCS-CGIC</u> ADCS-ADL BEHAVE-AD					1] 1.16 2] 1.04 3] 0.90 4] 1.90 1] 0.25 2] 0.34 3] 0.22 4] 0.33 1] -2.62 2] -2.79 3] -2.40 4] -3.13 1] 0.07 2] -0.72 3] -0.15 4] -0.26	5] 0.51 5] 0.63 5] 0.91 5] 0.35

EvTable131. Study results: Maprotiline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 8w**	
Fuchs 1993	OC Analysis 1] Placebo 2] Maprotiline 75 mg/d variable 3] Placebo change from baseline 4] Maprotiline change from baseline 5] Placebo vs. Maprotiline change from baseline	<u>Video rating of Global Impression</u> MMSE GDS	 1] 15.8 2] 15.0 1] 8.4 2] 8.2				3] 0.6 4] –0.2 1] 17.5 2] 15.3 1] 6.6 2] 5.3	5] 0.60 5] 0.22 5] 0.09

EvTable132. Study results: Minaprine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 60d		Final: (specify) 90d	
Passeri, 1998	Endpoint Analysis							
	1] Placebo SDAT patients	HDRS	1] 13 (7) 2] 15 (6) 3] 15 (5) 4] 13 (5)		1] 12 (7) 2] 11 (5) 3] 14 (4) 4] 8.8 (4)	5] <0.01 6] <0.01 7] <0.05 8] <0.01	1] 12 (7) 2] 10 (5) 3] 13(5) 4] 8.4 (5)	5] <0.05 6] <0.05 7] <0.01 8] <0.01
	2] Minaprine 50mg bid SDAT patients	SRT Anxiety	1] 5.5 (4.7) 2] 4.8 (3.7) 3] 5.5 (3.1) 4] 4.3 (2.9)		1] 4.8 (3.6) 2] 4.3 (3.7) 3] 4.2 (2.5) 4] 3.0 (1.8)	6] <0.05	1] 4.7 (3.5) 2] 3.6 (3.8) 3] 4.2 (2.4) 4] 2.7 (1.9)	5] <0.05 6] <0.05
	3] Placebo MID patients							
	4] Minaprine 50 mg bid MID patients	SRT Depression	1] 6.9 (5.2) 2] 6.9 (3.2) 3] 7.0 (3.6) 4] 7.6 (3.8)		1] 5.6 (4.4) 2] 4.8 (3.1) 3] 6.8 (4.2) 4] 4.8 (3.1)	5] <0.01 8] <0.01	1] 5.5 (4.7) 2] 4.4 (3.1) 3] 6.4 (4.0) 4] 3.8 (3.8)	6] <0.1 8] <0.01
	5] Minaprine vs. Placebo (SDAT)	SHGRS	1] 35 (8) 2] 34 (10) 3] 42 (11) 4] 38 (11)		1] 34 (8) 2] 33 (10) 3] 41 (11) 4] 35 (10)	6] <0.01	1] 34(8) 2] 32 (10) 3] 40 (12) 4] 34 (10)	6] <0.5 7] <0.01 8] <0.01
	6] Minaprine vs. Placebo (MID)	Nowlis	1] 14 (3.7) 2] 15 (4) 3] 16 (3.7) 4] 14 (3.8)		1] 14 (4) 2] 13 (3.9) 3] 15 (3.4) 4] 12 (2.8)	6] <0.01	1] 14 (4.1) 2] 13 (39) 3] 14 (2.9) 4] 12 (3.4)	5] <0.01 6] <0.01 7] <0.01 8] <0.01
	7] Minaprine vs. baseline (SDAT)							
	8] Minaprine vs. baseline (MID)							

EvTable133. Study results: Moclobemide.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 6w**	
Roth 1996	ITT Analysis 1] Placebo Difference from baseline 2] Moclobemide 400 mg/d Difference from baseline 3] Placebo vs. Moclobemide Change from baseline	HAM-D MMSE SCAG BGP CGAE Any improvement					1] 91 2] 12.6 1] 1.9 2] 2.6 1] 14.8 2] 17.3 1] 1.2 2] 1.6 1] 59% 2] 72%	3] 0.001 3] 0.05 3] NS 3] NS 3] <0.001

EvTable134. Study results: Naftidrofuryl.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) Response Rate no deterioration**	
Moller 2001	ITT Analysis 1] Placebo-response rate 2] Naftidrofuryl 400 mg/d – 3] Naftidrofuryl 600 mg/d – response rate 4] Placebo vs. Naftidrofuryl 400 mg 5] Placebo vs. Naftidrofuryl 600 mg/d 6] Naftidrofuryl 400 mg/d vs. 600 mg/d	<u>ADAS-cog & SCAG (positive response)</u> <u>ADAS-Cog</u> <u>SCAG</u> NOSGER CGI	 1] 28.6 (7.7) 2] 29.0 (8.5) 3] 29.5 (7.5) 1] 51.0 (8.3) 2] 52.3 (9.8) 3] 50.7 (8.6) 1] 69.6 (15.4) 2] 69.8 (14.3) 3] 66.2 (15.8)				 1] 58% 2] 75% 3] 73% 1] 67% 2] 84% 3] 73% 1] 65% 2] 84% 3] 84% 1] 50% 2] 63% 3] 58% 1] 55% 2] 73% 3] 66%	 4] 0.005 5] 0.015 6] 0.73 4] 0.003 5] 0.013 6] 0.61 4] 0.001 5] 0.001 6] 0.97 4] 0.049 5] 0.21 6] 0.49 4] 0.004 5] 0.10 6] 0.21

EvTable135. Study results: Olanzapine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6w	
Street 2000 Clarke 2001 Kennedy 2001 Mitzner 2001 Street 2001	ITT Analysis 1] Placebo change from baseline 2] Olanzapine 5mg/d change from baseline 3] Olanzapine 10mg/d change from baseline 4] Olanzapine 15mg/d change from baseline 5] Olanzapine 5mg/d vs. placebo 6] Olanzapine 10mg/d vs. placebo 7] Olanzapine 15mg/d vs. placebo	<u>NPI/NH Core total</u> BPRS total ADAS-Cog In sub-group with mild to moderate cognitive impairment					1] -3.7 (10.3) 2] -7.6 (7.7) 3] -6.1 (8.2) 4] -4.9 (7.8) 1] -1.4 (11.1) 2] -6.8 (8.6) 3] -5.6 (10.0) 4] -4.0 (10.9) 1] 1.38 (6.23) 2] -0.94 (8.10) 3] 4.00 (7.03) 4] 1.83 (8.98)	5] <0.001 6] 0.006 7] 0.24 5] 0.005 6] 0.06 7] 0.13 5] 0.703 6] 0.203 7] 0.695

EvTable136. Study results: Phosphatidylserine (PS).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3m**		**Final: (specify) 3m & 3m post**	
Amaducci 1988 SMID Group 1987	OC Analysis 1] Placebo moderate impairment 2] Placebo severe impairment 3] PS 200 mg/d moderate impairment 4] PS 200mg/d severe impairment 5] PS vs Placebo change from baseline severe impairment 6] PS vs placebo change from baseline moderate impairment	Set Test BDS Nonpersonal memory BDS part 2 Block tapping BDS Personal Memory BDS Daily Living Score	1] 27.57 2] 16.33 3] 26.02 4] 10.75 1] 3.00 2] 2.10 3] 3.23 4] 1.25 1] 19.40 2] 14.50 3] 19.27 4] 11.50 1] 1.38 2] 0.00 3] 1.03 4] 0.44 2] 5.5 4] 4.0 2] 15.6 4] 16.4		2] 11 4] 13 2] 2.0 4] 2.0	5] <0.10 6] NS 5] <0.10 6] NS 5] NS 6] NS 5] < 0.10 6] NS 2] 4.4 4] 4.4 2] 16.3 4] 16.6	1] 23.93 2] 9.22 3] 27.10 4] 15.63 1] 3.11 2] 1.20 3] 2.96 4] 1.25 1] 18.51 2] 10.40 3] 17.77 4] 14.25 1] 1.38 2] 0.11 3] 0.89 4] 1.25	5] <0.01 5] 0.05 5] 0.005 5] 0.05

EvTable137. Study results: Phosphatidylserine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 9w		Final: (specify) 12w	
Crook, 1992a	ITT Analysis 1] Placebo 2] Phosphatidylserine 100mg tid 3] Phosphatidylserine 100mg tid vs. Placebo	PRS-Concern of Memory F - Value PRS-Recall of Interviewer and staff F - Value PRS-Recall of past day F - Value PRS-Recall of past week F - Value PRS-Interviewer Notices memory Loss F - Value MAC-F First-last name test MAC-F Name-face association Memory for names of familiar persons Ability to recall the location of misplaced objects					3] 5.73 3] 4.92 3] 6.36 3] 9.76 3] 13.21 3] 12.29	3] 0.02 3] 0.04 3] 0.02 3] 0.01 3] 0.00 3] <0.00 3] <0.05 3] <0.05

EvTable138. Study results: Sertraline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 8w**	
Magai, 2000	ITT Analysis 1] Placebo 2] Sertraline 100 mg escalating 3] Difference between Placebo and Sertraline change from baseline	CSDD	1] 6.36 (2.13) 2] 5.76 (1.89)				1] 4.43 (1.95) 2] 3.53 (2.07)	3] NS
		GS	1] 0.93 (0.91) 2] 0.47 (0.87)				1] 0.57 (0.64) 2] 0.06 (0.24)	3] NS
		CMAI	1] 27.71(19.49) 2] 28.05(21.45)				1] 21.57(11.52) 2] 23.24(20.00)	3] NS
		AFBS	1] 2.29 (2.23) 2] 3.88 (2.64)				1] 1.71 (2.23) 2] 3.06 (2.73)	3] NS
		Knit-brow face	1] 4.86 (2.71) 2] 3.94 (3.07)				1] 4.43 (3.63) 2] 1.94 (2.65)	3] <0.1
		Sad face	1] 2.57 (2.27) 2] 2.65 (3.75)				1] 1.43 (1.74) 2] 2.18 (2.35)	3] NS

EvTable139. Study results: Sertraline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 6w		Final: (specify) 13w	
Lyketsos 2000	ITT Analysis 1] Placebo change from baseline 2] Sertraline 150 mg (escalating) change from baseline 3] Placebo vs. Sertraline change from baseline	<u>Psychiatrist rating of responders</u> CSDD HAM-D PDRS ADL subscale MMSE			 1] 2.7 (6.2) 2] -12.5 (7.0) 1] -4.4 (4.9) 2] -14.6 (10.0) 1] 0.7 (5.2) 2] -0.9 (4.7) 1] 0.3 (1.6) 2] -2.1 (5.0)	 1] <0.05 1] <0.05 2] <0.05	1] 10% 2] 75% 1] -2.6 (5.9) 2: -9.7 (8.3) 1] -3.4 (5.5) 2] -8.9 (12.4) 1] 3.4 (3.5) 2] -0.8 (5.2) 1] 0.8 (2.3) 2] -1.2 (4.7)	3] <0.05 3] 0.03 3] 0.20 3] 0.09 3] 0.18

EvTable140. Study results: Fluoxetine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify) 3m		Final] (specify) 6w	
Petracca 2001	ITT Analysis 1] Placebo 2] Fluoxetine 40 mg/d dose escalation 3] Placebo change from baseline 4] Fluoxetine change from baseline 5] Difference between Placebo and Fluoxetine change from baseline 6] Difference between Placebo and Fluoxetine	Ham-D CGI Severity Ham-A MMSE FIM	1] 17.2 (3.6) 2] 15.8 (2.1) 1] 3.0 (0.8) 2] 2.7 (0.9) 1] 9.1 (5.8) 2] 8.3 (5.1) 1] 23.2 (5.3) 2] 23.2 (4.5) 1] 64.2 (8.9) 2] 68.5 (3.4)				1] 10.0 (5.1) 2] 9.4 (5.7) 1] 2.4 (0.8) 2] 2.1 (0.7) 1] 6.2 (4.4) 2] 7.0 (5.6) 1] 23.9 (5.9) 2] 23.1 (6.8) 1] 67.1 (7.3) 2] 69.8 (2.8)	3] <0.001 4] <0.001 5] NS 6] NS 3] <0.001 4] <0.001 3] <0.001 4] <0.001 5] NS 6] NS 3] NS 4] NS 5] NS 6] NS 3] <0.01 4] <0.01 5] NS 6] NS

EvTable141. Study results: Haloperidol - Fluoxetine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify)		Final] (specify) 6 w	
Auchus 1996	OC Population 1] Placebo 2] Fluoxetine 20 mg/d 3] Haloperidol 3mg/d 4] Across group treatment effect	<u>CMAI</u>	1] 34.4 (8.2) 2] 33.8 (3.0) 3] 37.4 (4.4)				1] 33.0 (3.5) 2] 35.2 (10.3) 3] 35.0 (11.2)	4] 0.82
		BEHAVE-AD	1] 5.6 (3.4) 2] 7.0 (4.2) 3] 11.8 (4.9)				1] 6.6 (3.5) 2] 8.8 (3.5) 3] 9.2 (7.1)	4] 0.35
		CSI	1] 116.2 (57.0) 2]160.4(121.8) 3] 165.4 (50.3)				1] 134.8 (62.1) 2] 143.6 (79.3) 3] 179.4 (91.9)	4] 0.67

EvTable142. Study results: Risperidone.

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Katz, 1999 Jeste, 2000 Camilleri 2000	ITT Endpoint Analysis 1] Placebo 2] Risperidone 0.5 mg/d 3] Risperidone 1 mg/d 4] Risperidone 2 mg/d 5] Risperidone 0.5 mg/d vs Placebo 6] Risperidone 1 mg/d vs Placebo 7] Risperidone 2 mg/d vs Placebo 8] Placebo change from baseline 9] Risperidone 0.5 mg/d change from baseline 10] Risperidone 1 mg/d change from baseline 11] Risperidone 2 mg/d change from baseline	<u>BEHAVE-AD</u> CMAI Total CMAI Verbal CMAI Physical aggressive CGIC	1] 15.9 2] 15.9 3] 16.0 4] 15.4 1] 4.2 3] 4.2 4] 4.2				8] –4.2 (0.6)* 9] –4.8 (0.7)* 10] –6.5 (0.7)* 11] –6.4 (0.6)* 8] –0.50 9] –1.25 10] –1.80 11] –2.30 8] –2.1 9] –3.0 10] –5.4 11] –6.4 1] 3.7 2] 3.3 3] 3.2	5] 0.37 6] 0.002 7] 0.001 6] 0.006 7] <0.001 6] 0.002 7] <0.001

*SEM

EvTable143. Study results: Haloperidol - Trazodone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 16w**	
Teri, 2000	Efficacy Analysis 1] BMT 2] Haloperidol mean dose1.8 mg/d 3] Trazodone mean dose 200 mg/d 4] Placebo 5] Group Effect 6] Placebo vs Trazodone 7] Placebo vs Haloperidol 8] Placebo vs BMT 9] Traxodon vs Haloperidol 10] Trazodone vs BMT 11] Haloperidol vs BMT	ADCS-CGIC %improvement BRSD Change score MMSE Change score Lawton-Brody ADL Physical Change score Lawton-Brody ADL Instrumental Change score					1] 32% 2] 32% 3] 41% 4] 31% 1] –3.56 12.85) 2] –5.35(22.41) 3] –6.95(20.87) 4] -5.28 (24.36) 1] –0.05 (2.58) 2] –0.61 (2.69) 3] –1.97 (3.15) 4] –0.28 (3.35) 1] –0.27 (1.96) 2] 2.53 (4.00) 3] 1.62 (2.56) 4] 1.31 (2.47) 1] 0.17 (1.84) 2] 1.79 (3.20) 3] 1.81 (3.32) 4] 0.89 (3.32)	6] 0.99 7] 0.81 8] 0.65 9] 0.75 10] 0.52 11] 0.86 5] NS 6] NS 7] NS 8] NS 9] NS 10] <0.05 favours BMT 11] NS 6] <0.05 favours placebo 7] <0.05 favours placebo 6] <0.05 7] <0.05 favours placebo

EvTable143. Study results: Haloperidol - Trazodone cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify)		Final: (specify) 16w	
			SCB Subjective Screen for Caregiver Burden Subjective Objective					1] -2.95 (7.29 2] -1.88 (8.89) 3] -1.97 (10.06) 4] -2.58 (9.67) 1] -2.95 (7.29 2] -1.88 (8.89) 3] -1.97 (10.06) 4] -2.58 (9.67) 1] -1.23 (3.32) 2] -0.44 (3.22) 3] -1.14 (4.04) 4] -1.25 (4.02)	5] NS

EvTable144. Study results: Risperidone - Haloperidol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
DeDeyn 1999	ITT Population 1] Placebo 2] Haloperidol 1.2mg/d 3] Risperidone 1.1 mg/d 4] Risperidone vs Placebo 5] Risperidone vs Placebo change from baseline 6] Haloperidol vs Placebo change from baseline 7] Risperidone vs Placebo change from baseline	BEHAVE-AD total Behave-AD Aggressiveness CMAI total aggressive CMAI physical aggressive CMAI verbal aggressive CGI MMSE FAST Behave-AD % with > 30% reduction from baseline	1] 16.6 2] 16.5 3] 16.3 1] 5.0 2] 4.7 3] 5.0 1] 27.5 2] 26.3 3] 25.6 1] 19.7 2] 19.3 3] 18.9 1] 7.7 2] 7.0 3] 6.8				1] -4.2 2] -6.6 3] -5.2 1] -0.8 2] -1.6 3] -1.7 1] -1.6 2] -3.3 3] -3.9 1] -0.7 2] -0.3 3] -2.7 1] -0.8 2] -1.0 3] -1.2 1] 47% 2] 63% 3] 54%	4] 0.19 6] 0.01 4] 0.004 6] 0.01 7] 0.05 favors Risperidone 4] 0.01 7] 0.02 4] 0.01 7] 0.01 4] 0.01 5] <0.05 5] NS 5] NS 5] 0.25

EvTable145. Study results: Haloperidol - Tiapride.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 21 d	
Allain 2000	ITT Endpoint Analysis 1] Placebo 2] Tiapride 100-300 mg/d 3] Haloperidol 2-6 mg/d 4] Across treatment 5] Tiapride vs Placebo 6] Haloperidol vs Placebo 7] Tiapride vs Haloperidol 8] Placebo vs Tiapride change from baseline 9] Placebo vs Haloperidol change from baseline 10] Triapride vs Haloperidol change from baseline	<u>MOSES % responders (% with 25% decrease in irritability/ aggressiveness subscore)</u> MOSES Global Improvement very improved Global Improvement no change CGI MMSE	1] 20.28 (2.85) 2] 19.90 (2.92) 3] 20.52 (3.27)				1] 49% 2] 63% 3] 69% 1] 15.53 (5.25) 2] 13.33 (4.20) 3] 13.75 (4.59) 1] 14% 2] 24% 3] 31% 1] 21% 2] 12% 3] 12%	8] 0.04 9] 0.004 10] 0.38 5] 0.0009 6] 0.008 7] 0.53 4] NS 8] 0.03 9] 0.02 10] NS 8] NS 9] NS 10] NS

EvTable146. Study results: Olanzapine - Lorazepam.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 2h**		**Final: (specify) 24h**	
Meehan, 2002	OC Analysis 1]Placebo change from baseline 2] Olanzapine 2.5mg change from baseline 3] Olanzapine 5mg change from baseline 4] Lorazepam 1mg change from baseline 5] Olanzapine 2.5mg vs. placebo 6] Olanzapine 5mg vs. placebo 7] Lorazepam 1mg vs. placebo	<u>PANSS-EC</u> CMAI ACES BPRS Total BPRS Positive CGI-S MMSE Total			1] -5.27 (6.87) 2] -7.86 (6.05) 3] -8.67 (6.97) 4] -8.49 (6.55) 1] -2.78 (3.4) 2] -3.77 (2.93) 3] -3.97 (3.89) 4] -4.18 (3.52) 1] 1.04 (1.66) 2] 1.80 (1.61) 3] 1.88 (1.86) 4] 2.19 (1.83)	5]<0.05 6]<0.01 7]<0.01 5] NS 6]<0.05 7]<0.05 5]<0.05 6]<0.01 7]<0.01	1] -3.81 (6.20) 2] -6.44 (6.00) 3] -6.29 (6.75) 4] -5.75 (5.99) 1] -2.21 (3.7) 2] -2.82 (3.21) 3] -3.36 (3.92) 4] -2.82 (3.08) 1] 0.63 (1.14) 2] 0.90 (1.19) 3] 1.29 (1.49) 4] 1.07 (1.12) 1]-10.29(11.72) 2]-10.51(11.50) 3]-10.59(11.31) 4]- 9.12(10.27) 1] -2.09 (3.80) 2] -1.72 (3.50) 3] -1.86 (3.39) 4] -1.32 (3.32) 1] -0.59 (0.92) 2] -0.38 (0.80) 3] -0.47 (0.89) 4] -0.46 (0.80) 1] 0.37 (3.62) 2] 0.31 (2.29) 3] 0.10 (3.01) 4] 0.08 (3.04)	5]<0.05 6]<0.05 7] NS 5] NS 6] NS 7] NS 5] NS 6] <0.01 7] <0.05 5] NS 6] NS 7] NS 5] NS 6] NS 7] NS 5] NS 6] NS 7] NS

EvTable147. Study results: Thoridazine - Loxapine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 8w	
Barnes 1981	Endpoint Analysis							
	1] Placebo	BPRS Total					1] 39.74 2] 39.73 3] 36.89	4] <.05 5] <.05 6] <.01 7] NS 8] NS
	2] Thoridazine 62.5mg/d							
	3] Loxapine 10.5mg/d	SCAG					1] 59.24 2] 58.82 3] 53.58	4] <.05 5] <.05 6] <.01 7] NS 8] NS
	4] Improvement from baseline Placebo							
	5] Improve from baseline Thoridazine	CGI-Improvement					1] 3.41 2] 3.18 3] 3.11	7] NS 8] NS
	6] Improve from baseline Loxapine	NOSIE						7] NS 8] NS 9] NS
	7] Thioridazine vs Placebo from baseline	CGI Severity					1] 3.17 2] 3.07 3] 3.05	4] NS 5] <0.01 6] <0.01
	8] Loxapine vs Placebo from baseline							
	9] Loxapine vs Thioridazine from baseline							

EvTable148. Study results: Citalopram.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) up to 17d	
Pollock, 2002	ITT Analysis 1] Placebo 2] Citalopram 20 mg/d 3] Perphenazine 0.1mg/kg/d 4] Citalopram vs. placebo 5] Perphenazine vs. placebo	Neuro-Behavioural Rating Score	1] 58.3 (11.9) 2] 53.5 (10.2) 3] 57.1 (14.0)				1] 56.0 (15.2) 2] 43.5 (12.1) 3] 49.9 (14.2)	4] 0.002 5] 0.14

EvTable149. Study results: Xanomeline Tartrate (XT).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6m	
Bodick 1997 Veroff, 1998 Satlin 1997	Endpoint analysis 1] Placebo change from baseline 2] XT 25 mg tid change from baseline 3] XT 50 mg tid change from baseline 4] XT 75 mg tid change from baseline 5] XT 25 mg tid difference from Placebo 6] XT 50 mg tid difference from Placebo 7] XT 75 mg tid difference from Placebo 8] Dose response	ADAS-Cog CIBIC+ ADSS NOSGER IADL CNTB					1] 1.42 2] 1.03 3] 0.38 4] -1.42 1] 4.33 2] 4.44 3] 4.09 4] 4.00 1] 1.15 2] 0.06 3] -1.49 4] -1.69 1] 0.48 2] 0.58 3] -0.29 4]-0.12 4] 2.77	5] 0.935 6] 0.367 7] 0.045 8] 0.033 5] 0.846 6] 0.036 7] 0.022 8] 0.005 8] 0.002 5] 0.457 6] 0.078 7] 0.032 8] 0.018 5] 0.786 6] 0.088 7] 0.026 8] 0.010 7] 0.039

EvTable150. Study results: Haloperidol - Risperidone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12 w**	
Chan 2001	OC Analysis 1] Haloperidol 0.5-2 mg/d 2] Risperidone 0.5-2 mg/d 3] Haloperidol change from baseline 4] Risperidone change from baseline 5] Between treatments	CMAI BEHAVE-AD (Aggressive-ness) FAST CMMSE	1] 46.4 (10.5) 2] 48.9 (14.5) 1] 2.1 (2.0) 2] 2.2 (2.5) 1] 8.2 (5.0) 2] 7.9 (6.0)				1] 36.3 (10.4) 2] 40.8 (16.9) 1] 0.8 (1.5) 2] 0.9 (2.0) No data extracted 3] –0.15 4] –0.42	3] 0.000 4] 0.002 5] 0.95 3] 0.011 4] 0.019 5] 0.56 3] 0.84 4] 0.70

EvTable151. Study results: Fluoxetine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 30d**		**Final: (specify) 45d**	
Taragano 1997	OC Analysis 1] Fluoxetine 10 mg/d 2] Amitriptyline 25 mg/d 3] Between treatments	Ham-D MMSE	1] 25.3 (3.8) 2] 26.3 (4.0) 1] 20.0 (3.2) 2] 18.8 (4.2)	3] 0.10 3] 0.10	1] 19.3 (3.2) 2] 17.8 (2.5)	3] 0.10	1] 16.7 (2.9) 2] 15.6 (3.2) 1] 21.4 (2.9) 2] 21.5 (3.5)	3] 0.10 3] 0.10

EvTable152. Study results: Lorazepam, Alprazolam.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 28d	
Ancill, 1991	OC Analysis 1] Lorazepam mean 3.1 mg/d 2] Alprazolam mean 1.5 mg/d 3] Lorazepam vs Alprazolam	CGI % improved					1] 29% 2] 42%	3] NS

EvTable153. Study results: Citalopram.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 6w		Final: (specify) 12w	
Karlsson, 2000	OC Analysis 1] Citalopram 40 mg variable 2] Mianserin 60 mg variable 3] Citalopram vs. Mianserin from baseline	MADRS	1] 26 2] 27		1] 18 2] 18		1] 15 2] 16	3] >0.7

EvTable154. Study results: Haloperidol – Oxazepam - Diphenhydramine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point:**		**Final: 8w**	
Coccaro 1990	Completers Analysis 1] Haloperidol 5 mg/d (max) 2] Oxazepam 60 mg/d (max) 3] Diphenhydramine 200 mg/d (max) 4] Between groups, change from baseline 5] Change from baseline 6] Between groups at timepoint	CDRS mean score ADAS BPRS PSMS NOSIE	1] 2.78 2] 2.76 3] 2.66 1] 11.00 (5.95) 2] 11.50 (4.90) 3] 9.82 (3.68) 1] 6.33 (3.01) 2] 5.81 (2.17) 3] 5.67 (2.72) 1] 42.17 (12.95) 2] 45.75 (11.02) 3] 39.35 (10.36) 1] 78.19 (7.67) 2] 80.69 (9.10) 3] 73.47 (5.88)	4] > 0.10			1] 8.39 (6.09) 2] 9.12 (4.33) 3] 6.12 (4.78) 1] 4.78 (2.44) 2] 5.50 (2.71) 3] 4.47 (2.85) 1] 37.89 (15.36) 2] 43.68 (11.47) 3] 34.76 (9.94) 1] 78.31 (9.45) 2] 80.69 (9.89) 3] 73.00 (11.53)	4] NS 5] < 0.001 6] NS 4] NS 5] < 0.02 6] NS 4] NS 5] < 0.001 6] NS 4] NS 5] NS 6] <0.02

EvTable155. Study results: Loxapine - Haloperidol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 14d		Final: (specify) 28d	
Carlyle 1993	OC Analysis 1] Haloperidol 7.0 mg/d (mean) 2] Loxapine 36.0 mg/d (mean) 3] Difference between Haloperidol and Loxapine	Mean Aggression Score for responders Mean depression score Response rate	1] 6.0 2] 8.6		1] 4.8 2] 6.6	3] NS	1] 2.5 2] 4.2 1] 11/14 2] 14/17	3] NS 3] NS

EvTable156. Study results: 5'-MTHF - Trazodone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 4w**		**Final: (specify) 8w**	
Passeri 1992	OC Analysis							
	1] 5'-MTHF 50 mg/d	HDRS	1] 23 (5) 2] 23 (3) 5] 23 (5) 6] 23 (4) 9] 21 (5) 10] 23 (3)		1] 20(6) 2] 21 (4) 5] 21 (6) 6] 21 (5) 9] 17 (7) 10] 22 (2)	3] <0.01 4] <0.05 7] <0.01 8] <0.01	1] 18 (6) 2] 19 (5) 5] 18 (6) 6] 19 (6) 9] 18 (5) 10] 20 (3)	3] <0.01 4] <0.01 7] <0.01 8] <0.01 11] <0.01
	2] Trazodone 100mg/d							
	3] 5'-MTHF change from baseline							
	4] Trazodone change from baseline	RVM immediate recall	1] 20 (7) 2] 22 (9) 5] 20 (7) 6] 22 (9) 9] 20 (8) 10] 20 (8)				1] 23 (8) 2] 22 (9) 5] 23 (7) 6] 22 (8) 9] 22 (7) 10] 22 (11)	3] <0.01 7] <0.01
	5] 5'-MTHF subgroup AD							
	6] Trazodone subgroup AD							
	7] 5'-MTHF change from baseline subgroup AD	RVM delayed recall	1] 2 (2) 2] 3 (2) 5] 3 (2) 6] 3 (2) 9] 2 (2) 10] 4 (2)				1] 3 (2) 2] 3 (2) 5] 3 (2) 6] 3 (2) 9] 3 (2) 10] 3 (2)	
	8] Trazodone change from baseline subgroup AD							
	9] 5'-MTHF subgroup MID							
	10] Trazodone subgroup MID							
	11] Trazodone change from baseline subgroup MID							

EvTable157. Study results: Tiapride - Melperone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 28d**	
Gutzmann 1997	ITT Analysis 1] Melperone 400 mg/d 2] Tiapride 100 mg/d 3] Melperone vs Tiapride change from baseline	CGI (item 1) Severity of illness % Severely Ill or markedly Ill	1] 68% 2] 77%				1] 35.9% 2] 52.6%	
		CGI (Item 2) global change % responders					1] 72.5% 2] 73.4%	3] 0.675
		NOSIE social competence	1] 28.5 2] 29.2				1] 32.0 2] 31.4	
		NOSIE irritability	1] 30.9 2] 32.1				1] 25.7 2] 26.8	
		AGGR	1] 10.6 2] 11.0				1] 5.7 2] 4.8	
		VAS-ADL	1] 31.1 2] 32.5				1] 41.8 2] 39.9	
		VAS- verbal aggression	1] 28.5 2] 30.9				1] 14.7 2] 15.8	
		VAS-aggressive behaviour	1] 26.9 2] 38.4				1] 16.5 2] 18.3	

*SEM

EvTable158. Study results: Imipramine - Paroxetine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 8w	
Katona, 1998	ITT Analysis 1] Paroxetine 50 mg bid variable change from baseline 2] Imipramine 50 mg bid variable change from baseline 3] Difference between Paroxetine group and Imipramine group	<u>MADRS</u> <u>CGI severity of Illness</u> CGI improvement Score CSDD GBS total score					1] -12.6 (10.0) 2] -11.8 (10.0) 1] -1.3 (1.5) 2] -1.3 (1.5) 1] 2.7 (1.5) 2] 2.7 (1.6) 1] -8.9 (6.7) 2] -7.1 (7.5) 1] -11.7 (18.1) 2] -12.0 (19.6)	3] >0.368 3] >0.286 3] <0.049 favours Paraxetine 3] >0.651

EvTable159. Study results: Loxapine - Haloperidol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: 10w**	
Petrie, 1982	Efficacy Analysis Population 1] Placebo 2] Haloperidol 10 mg/d (max) 3] Loxapine 50 mg/d (max) 4] Haloperidol vs baseline 5] Loxapine vs baseline 6] Placebo vs Haloperidol change from baseline 7] Placebo vs Loxapine change from baseline	CGIC (marked or moderate improvement) BPRS total SCAG total NOSIE	1] 46.36 2] 46.35 3] 50.79 1] 61.0 2] 55.9 3] 62.9 1] 157.2 2] 184.0 3] 155.0				1] 9% 2] 35% 3] 32% 1] 48.90 2] 39.60 3] 43.84 1] 60.9 2] 47.3 3] 54.4 1] 151.2 2] 192.0 3] 171.4	4] < 0.05 5] < 0.05 6] <0.05 7] <0.05 4] < 0.05 5] < 0.05 5] < 0.05

EvTable160. Adverse events. Various cholinergic neurotransmitter modifying agents.

Adverse events (AE) identified in included studies	ALAPROCLATE Dehlin, 1985	ANAPSOS Alvarez, 2000	BMY Cutler, 1993	**CARBAMAZEPINE** Olin, 2001	**CARBAMAZEPINE** Tariot, 1998	CITALOPRAM Nyth, 1990	DIVALPROEX Porsteinsson, 2000	DIVALPROEX Tariot, 2001b	FLUOXETINE Petracca, 2001	FLUOXETINE Taragano, 1997
Withdrawn (%) due to AE	T: 0 C: 13	T: 7 C: 7	T: 24 C: 9	T: 0 C: 25	T: 15 C: 0	T: 24 C: 14	T: 7 C: 14	T: 22 C: 4	T: 6 C: 4	T: 58 C: 22
AE Checklist (Max 5)	2	3	1	4	4	3	5	5	5	3
None Reported			x							
Balance	x	x			x					
Accidental Injury								S		
Dizziness	x	x				X			X	
Falls		x			NS					
Behavioral		x								
Agitation	x						x			
Cardiovascular							x	S		
Arrhythmia		x				NS				
Hypotension	x				S					
Hypertension										
Extrapyramidal					NS					
Tremor									X	
Gastrointestinal					NS			x	X	
Abdominal pain										
Constipation									X	X
Diarrhea	x			x			x			X
Dyspepsia									X	
Nausea, vomiting		x		x			x	NS		X
Metabolic/nutritional								NS		
Eating disorder								NS		
Weight Change								NS		
Neurological							x			
Asthenia										
Psychiatric	x	x				X				
Anxiety										
Confusion, delirium	x				NS		x		X	X
Depression	x					X				
Respiratory							x			
Cough, cold, infection										
Rhinitis										
Other	x					X	S	NS	X	
Aberrant hematology				NS			NS	S		
Fatigue, weakness					NS	X	x			
Fever, flu, pneumonia					NS		x			
Headache										
Hepatic abnormality										
Muscle/joint disorder	x						x			
Pain										
Rash, skin disorder		x			NS	X	x	NS		
Sleep disorder	x				NS	X	x	S		
Urinary disorder					NS		x	NS		

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable160. Adverse events. Various cholinergic neurotransmitter modifying agents cont'd.

Adverse events (AE) identified in included studies	**FLUVOXAMINE** Olafsson, 1992	**IMIPRAMINE** Reifler, 1989	**LISURIDE** Claus, 1998	**LU 25-109** Thal, 2000b	**MAPROTILINE** Fuchs, 1993	**MINAPRINE** Passeri, 1987	**MOCLOBEMIDE** Roth, 1996	**NAFTIDROFURYL** Moller, 2001
Withdrawn (%) due to AE	T: 18 C: 33	T: 15 C: 3	T: 0 C: 0	T: 30 C: 12	T: 2 C: 2	T: 0 C: 0	T: NR C: NR	T: 0 C: 0
AE Checklist (Max 5)	2	2	1	1	3	5	2	2
None Reported								
Balance						x		
Accidental Injury								
Dizziness		NS	x	x	NS		NS	
Falls								
Behavioral	x							
Agitation				x		x	NS	
Cardiovascular		x						x
Arrhythmia							NS	
Hypotension								
Hypertension					NS		NS	
Extrapyramidal								
Tremor								
Gastrointestinal							NS	
Abdominal pain				x			NS	
Constipation					x		NS	
Diarrhea				x			NS	
Dyspepsia						x		
Nausea, vomiting	x			x	x		NS	
Metabolic/nutritional		x		x				
Eating disorder				x				
Weight Change				x	NS		NS	
Neurological								
Asthenia				x				
Psychiatric	x				x			
Anxiety		x				x	x	
Confusion, delirium				x				
Depression	x			x				
Respiratory								
Cough, cold, infection								
Rhinitis								
Other		x		x	x		NS	x
Aberrant hematology								
Fatigue, weakness			x	x	x		NS	
Fever, flu, pneumonia		x						
Headache			x	x		x	x	
Hepatic abnormality								
Muscle/joint disorder							NS	
Pain								
Rash, skin disorder						x		
Sleep disorder	x	NS		x			NS	
Urinary disorder				x	x			

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable160. Adverse events. Various cholinergic neurotransmitter modifying agents cont'd.

Adverse events (AE) identified in included studies	**OLANZEPINE** Street, 2000	**PHOSPHATIDYL-SERINE** Amaducci, 1988	**PHOSPHATIDYL-SERINE** Crook, 1992a	**RISPERIDONE** Katz, 1999	**SERTRALINE** Magai, 2000	**SERTRALINE** Lyketsos, 2000	**XANOMELINE** Bodick, 1997
Withdrawn (%) due to AE	T: 12 C: 4	T: 0 C: 0	T: 0 C: 0	T: 16+ C: 12	T: 12 C: 14	T: 0 C: 0	T: 40+ C: 35
AE Checklist (Max 5)	2	3	4	4	5	2	2
None Reported		x	x				
Balance	S*						
Accidental Injury	NS*			X			
Dizziness							
Falls				X			
Behavioral							
Agitation	NS*			X	x	NS	
Cardiovascular							
Arrhythmia							
Hypotension							
Hypertension							
Extrapyramidal				X			
Tremor						NS	
Gastrointestinal						NS	
Abdominal pain							
Constipation							
Diarrhea							
Dyspepsia							S*
Nausea, vomiting							S*
Metabolic/nutritional							S*
Eating disorder	NS*						
Weight Change	NS*						
Neurological							
Asthenia							
Psychiatric							
Anxiety	NS*						
Confusion, delirium					x	x	
Depression							
Respiratory				X			
Cough, cold, infection	NS*			X			
Rhinitis				X			
Other	NS*			X	x		S*
Aberrant hematology							
Fatigue, weakness							
Fever, flu, pneumonia	NS*			X			
Headache							
Hepatic abnormality							
Muscle/joint disorder							
Pain	NS*			X			S*
Rash, skin disorder	NS*			X			
Sleep disorder	S*			X			
Urinary disorder				X			

NR = # Withdrawals due to adverse events Not Reported; + = Dose Effect on Adverse Events
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable160. Adverse events. Various cholinergic neurotransmitter modifying agents cont'd.

Adverse events (AE) identified in included studies	**LORAZEPAM (T) ALPRAZOLAM (C)** Ancill, 1991	**HALOPERIDOL (T1) OXAZEPAM (T2) DIPHENHYD (T3)** Coccaro, 1990	**HALOPERIDOL (T) LOXAPINE (C)** Carlyle, 1993	**HALOPERIDOL (T1) LOXAPINE (T2) PLACEBO (C)** Patria, 1982	**5'-MTHF (T) TRAZODONE (C)** Passeri, 1993	**TIAPRIDE (T) MELPERONE (C)** Gutzmann, 1997	**HALOPERIDOL (T1), BMT (T2), TRAZODONE (T3)** Teri, 2000
Withdrawn (%) due to AE	T: 19 C: 11	T1: 10 T2: 11 T3: 5	T: 20 C: 15	T1: 21 T2: 15 C: 5	T: 0 C: 0	T: 11 C: 6	T1: NR T2: NR T3: NR
AE Checklist (Max 5)	4	3	5	5	3	5	2
None Reported							
Balance					x		S*
Accidental Injury							
Dizziness						x	NS*
Falls			x				
Behavioral	NS*			NS*			
Agitation	NS*	x				x	
Cardiovascular				x			
Arrhythmia							
Hypotension	S*		x	x			
Hypertension						x	
Extrapyramidal		x	x	x		x	S*
Tremor			x				NS*
Gastrointestinal				x		x	
Abdominal pain							
Constipation			x				
Diarrhea							
Dyspepsia							
Nausea, vomiting						x	
Metabolic/nutritional						x	
Eating disorder							
Weight Change						x	
Neurological	S*			x		x	
Asthenia							
Psychiatric							
Anxiety							
Confusion, delirium	S*		x				
Depression						x	
Respiratory							
Cough, cold, infection							
Rhinitis							
Other	S*	x	x	S*	x	x	NS*
Aberrant hematology							
Fatigue, weakness						x	NS*
Fever, flu, pneumonia						x	
Headache							
Hepatic abnormality							
Muscle/joint disorder							
Pain							
Rash, skin disorder							
Sleep disorder						x	
Urinary disorder			x			x	

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable160. Adverse events. Various cholinergic neurotransmitter modifying agents cont'd.

Adverse events (AE) identified in included studies	**HALOPERIDOL(T1) FLUOXETINE (T2) PLACEBO (C)** Auchus, 1997	**CITALOPRAM (T) MIANSERIN (C)** Karlsson, 2000	**PERPHENAZINE CITALOPRAM** Pollock, 2002	**TIAPRIDE (T1) HALOPERIDOL (T2) PLACEBO (C)** Allain, 2000	**HALOPERIDOL (T) RISPERIDONE (C)** Chan, 2001	**HALOPERIDOL (T1) RISPERIDONE (T2) PLACEBO (C)** De Deyn, 1999	**CITALOPRAM (T1) PERPHENAZINE (T2) PLACEBO** [illegible]
Withdrawn (%) due to AE	T1: 33 T2: 0 C: 17	T: 5 C: 9	T:NR C:NR	T1: 5 T2: 17 C: 6	T: 4 C: 7	T1: NR T2: NR C: NR	
AE Checklist (Max 5)	3	3	2	3	1	1	
None Reported							
Balance	x						
Accidental Injury						NS*	
Dizziness		NS*					
Falls						NS*	
Behavioral				x			
Agitation		NS*	S*			NS*	
Cardiovascular				x			
Arrhythmia							
Hypotension				x	NS*		
Hypertension				x			
Extrapyramidal			NS*	S*	S*		
Tremor	x			x			
Gastrointestinal							
Abdominal pain							
Constipation		NS*		x	x		
Diarrhea				x			
Dyspepsia		x					
Nausea, vomiting		NS*		x	x		
Metabolic/nutritional							
Eating disorder							
Weight Change							
Neurological			NS*				
Asthenia				x			
Psychiatric							
Anxiety	x	NS*		x			
Confusion, delirium	x						
Depression	x						
Respiratory							
Cough, cold, infection							
Rhinitis							
Other				NS*			
Aberrant hematology							
Fatigue, weakness		S*					
Fever, flu, pneumonia							
Headache		NS*					
Hepatic abnormality							
Muscle/joint disorder							
Pain		NS*					
Rash, skin disorder							
Sleep disorder		S*		x	x	NS*	
Urinary disorder		x		x			

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable160. Adverse events. Various cholinergic neurotransmitter modifying agents cont'd.

Adverse events (AE) identified in included studies	**PAROXETINE (T) IMIPRAMINE (C)** Katona, 1998	**OLANZEPINE (T) LORAZEPAM (C)** Meehan, 2002	**THIORIDAZINE (T1) LOXAPINE (T2) PLACEBO (C)** Barnes, 1982
Withdrawn (%) due to AE	T: 18 C: 17	T: 0 C: 0	T1: 18 T2: 21 C: 12
AE Checklist (Max 5)	4	3	3
None Reported			
Balance			
Accidental Injury		NS*	
Dizziness			
Falls			
Behavioral			
Agitation			x
Cardiovascular		NS*	x
Arrhythmia		NS*	
Hypotension			x
Hypertension		NS*	x
Extrapyramidal		NS*	x
Tremor			
Gastrointestinal			
Abdominal pain			
Constipation			
Diarrhea			
Dyspepsia			
Nausea, vomiting	x		
Metabolic/nutritional			
Eating disorder			
Weight Change			
Neurological			
Asthenia	x		
Psychiatric	x		
Anxiety			
Confusion, delirium	x		
Depression			
Respiratory	x		
Cough, cold, infection			
Rhinitis			
Other	x		x
Aberrant hematology			
Fatigue, weakness			x
Fever, flu, pneumonia			
Headache		NS*	
Hepatic abnormality			
Muscle/joint disorder			
Pain			
Rash, skin disorder			
Sleep disorder	x	NS*	
Urinary disorder			

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable161. Key characteristics: Cerebrolysin (CERE).

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Bae 2000	IF	7	Placebo Cerebrolysin	NINCDS	AD	Mild-Mod	53	53	71.0y (NR) 34%M	30 ml/d 5 d/w	4w	ADAS-Cog Katz-ADL CGIS/C GDS Lawton-IADL MMSE	No
Panisset 2002	NI	8	Placebo Cerebrolysin	NINCDS	AD	Probable Mild-Mod	192	171	74.1y (59-81y) 42%M 93.5% White	30 ml/d 5 d/w	6m	ADAS-cog CIBIC+ MMSE DAD CORNELL PSMS IADL Behave-AD CDR CMH Trail Making Test	APOE Genotype
Ruether 1994 Auxiliary: Ruether 2000	NR	7	Placebo Cerebrolysin	DSM-III-R	AD	Mild-Mod	120	120	71.5y (NR) 34%M	30 ml 5d/wk	28d	BF-S GDS Ham-D MMSE NAI SCAG Trail Making ZVT-G	No

EvTable161. Key characteristics: Cerebrolysin (CERE) cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Ruether 2001 Auxiliary: Ruether 2002	IF	8	Placebo Cerebrolysin	NINCDS ICD I0	AD	Probable Mild-Mod	149	136	73.0y (50-85y) 42%M	30ml Cere 70ml Saline 5d/w	16w	ADAS-Cog ADAS-Noncog CGI MADR-S NAI SKT	MMSE
Xiao 1999	IF	6	Placebo Cerebrolysin	DSM IV	VaD	Mild-Modly Sev	148	147	69.7y (55-85y) 69%M	30 ml/d 5d/wk	4w	ADL CGI Ham-D MMSE NAI SCAG Trail Making ZVT	No
Xiao 2000	IF	7	Placebo Cerebrolysin	DSM-III-R NINCDS	AD	Mild-Modly Sev	157	155	70.3y (55-85y) 50%M	30 ml 5d/w	4w	ADL CGI HAM-D MMSE NAI SCAG ZVT	No

EvTable162. Study results: Cerebrolysin (CERE).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 4w**	
Bae, 2000	ITT Analysis 1] Placebo 2] CERE 30 ml IV qid 3] Placebo change from baseline 4] CERE change from baseline 5] CERE vs Placebo change from baseline	<u>ADAS-Cog</u> <u>CGIS/C (Improved)</u> MMSE GDS KATZ ADL LAWTON IADL	1] 33.51 (13.35) 2] 32.52 (14.65) 1] 14.6 (5.5) 2] 16.3 (4.8) 1] 7.1 (3.4) 2] 6.1 (2.9) 1] 9.9 (3.2) 2] 9.1 (3.4) 1] 25.2 (5.9) 25.5 (6.4)				3] –0.36 (3.59) 4] –3.23 (4.75) 1] 21.1% 2] 61.8% 3] 0.21 4] 1.68	5] 0.02 5] 0.01 5] 0.04 5] NS 5] NS 5] NS

EvTable163. Study results: Cerebrolysis (CERE).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3m**		**Final: (specify) 6m**	
Panisset, 2002	OC Analysis 1] Placebo mean change from baseline 2] CERE 30 ml 5d/w for 4 weeks mean change from baseline 3] CERE vs. Placebo change from baseline	 CIBIC+ ADAS-Cog DAD MMSE	 1] 23.63 (1.53) 2] 24.20 (1.68) 1] 20.93 (0.33) 2] 20.22 (0.34)		Endpoint 2 months after end of therapy 1] 4.29 (0.11)* 2] 4.08 (0.10) 1] -0.88 (0.61) 2] 0.04 (0.62) 1] -2.34 (1.4) 2] -1.54 (1.38) 1] 0.17 (0.34) 2] -0.06 (0.34)	 3] 0.033 3] 0.284 3] 0.680 3] 0.620	5 months after end of therapy 1] 4.46 (0.12) 2] 4.42 (0.12) 1] 1.02 (0.69) 2] 2.83 (0.68) 1] -4.08(1.63) 2] -6.04 (1.60) 1] -0.34 (0.39) 2] -0.93 (0.38)	

EvTable164. Study results: Cerebrolysin (CERE).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 4w**	
Ruether, 1994 Ruether, 2000	ITT Analysis 1] Placebo 2] CERE 30 ml 5d/w for 4 weeks 3] CERE 30 ml vs baseline 4] Cere vs. Placebo change from baseline	<u>ZVT-G</u> <u>SCAG</u> <u>CGI % with improvement</u> NAI Bf-S	1] 184.4 (39.3) 2] 184.1 (32.4) 1] 66.9 (7.5) 2] 66.5 (6.5) 1] 48.2 (2.7) 2] 48.1 (2.2) 1] 44.7 (3.6) 2] 43.7 (4.3)				1] 185.6 (21.5) 2] 161.5 (22.8) 1] 65.8 (6.1) 2] 49.8 (5.2) 1] 20% 2] 100% 1] 45.6 (3.3) 2] 34.5 (2.1) 1] 41.6 (5.7) 2] 26.9 (6.7)	3] <0.05 4] <0.0001 3] <0.05 4] <0.0001 3] 0.0001 4] <0.0001 3] <0.05 4] NS 3] <0.05

EvTable165. Study results: Cerebrolysin (CERE).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 16w Endpoint**		**Final: (specify) 28w Follow-up**	
Ruether 2001 Ruether 2002	ITT Analysis 1] Placebo 2] CERE 30 ml/d 5d/w for 4 weeks (repeat after 8w washout) 3] Placebo change from baseline 4] CERE 30 ml/d change from baseline 5] CERE vs Placebo change from baseline 6] Mean treatment difference between CERE and Placebo	<u>CGI</u> <u>ADAS-Cog</u> NAI ADAS-Noncog MADR-S SKT	1] 5.16 (0.07) 2] 5.24 (0.07) 1] 30.21 (1.57) 2] 32.01 (1.44)		3] 4.60 (0.11) 4] 4.18 (0.11) 3] 1.1 (0.59) 4] -2.1(0.69) 3] 0.0 (0.21) 4] -0.5 (0.29) 3] -0.2 (0.29) 4] -1.2 (0.45)	6] .004 5] .001 5] 0.07 6] .003 5] NS 5] NS	3] 4.86 (0.12) 4] 4.81 (0.12) 3] 1.6 (0.59) 4] 0.0 (0.65) 3] 0.4(0.30) 4] 0.0 (0.32) 3] 0.9 (0.37) 4] -0.1(0.38)	6] <0.024 5]<0.025 6] 0.024 5] 0.071 5]<0.025 6] 0.003 5] 0.102 5] 0.161

EvTable166. Study results: Cerebrolysin (CERE).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 2w**		**Final: (specify) 4w**	
Xiao, 1999	ITT Analysis 1] Placebo 2] CERE30 ml QID 5d/w 3] CERE vs Placebo change from baseline	<u>MMSE</u>	1] 20.08 (3.58) 2] 19.61 (3.31)		1] 21.01 (4.57) 2] 20.96 (3.74)	3] 0.252	1] 21.80 (4.17) 2] 22.29 (4.19)	3] 0.028
		<u>CGI improved</u>			1] 61% 2] 48%	3] 0.19	1] 71% 2] 73%	3] 0.11
		HAM-D	1] 8.47 (4.83) 2] 9.68 (4.95)		1] 7.33 (4.73) 2] 7.56 (5.24)	3] 0.078	1] 6.33 (3.94) 2] 6.68 (5.86)	3] 0.179
		SCAG	1] 43.55(12.23) 2] 44.06(12.16)		1] 40.20(11.20) 2] 39.74(11.47)	3] 0.359	1] 36.94(11.63) 2] 37.00(12.68)	3] 0.767
		ADL	1] 30.50 (8.25) 2] 30.92 (9.05)		1] 29.40 (8.82) 2] 30.45 (9.82)	3] 0.429	1] 28.34 (8.95) 2] 29.53(10.34)	3] 0.377
		NAI	1] 45.94 (6.39) 2] 46.44 (6.51)		1] 45.60 (6.90) 2] 45.88 (6.58)	3] 0.756	1] 45.36 (6.92) 2] 45.11 (7.09)	3] 0.355
		ZVT-1	1] 182.96 (95.77) 2] 204.69 (122.27)		1] 166.81 (84.30) 2] 165.00 (92.05)	3] 0.125	1] 170.45 (93.54) 2] 159.63 (85.33)	3] 0.017
		ZVT-2	1] 177.88 (107.90) 2] 209.23 (163.85)		1] 166.28 (92.93) 2] 170.74 (114.50)	3] 0.193	1] 170.05 (93.86) 2] 159.00 (95.88)	3] 0.016

EvTable167. Study results: Cerebrolysin (CERE).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 4w**	
Xiao, 2000	ITT Analysis 1] Placebo IV 2] CERE IV 30 ml qid, 4d/w 3] CERE IV vs Placebo change from baseline	<u>CGI</u> <u>% improved</u>			1] 52% 2] 39%	3] 0.03 favours placebo	1] 60% 2] 72%	3] 0.02
		<u>MMSE</u>	1] 19.3 (3.2) 2] 18.81 (2.32)		1] 20.12(4.16) 2] 20.05(3.37)	3] 0.417	1] 20.57 (4.61) 2] 21.26 (4.08)	3] 0.043
		HAM-D	1] 7.16 (5.02) 2] 7.04 (4.93)		1] 6.26 (4.48) 2] 6.50 (4.63)	3] 0.403	1] 5.56 (4.16) 2] 5.29 (4.97)	3] 0.783
		SCAG	1] 42.07(12.44) 2] 41.91(11.99)		1] 39.73(12.73) 2] 37.87(12.12)	3] 0.025	1] 38.66(12.64) 2] 35.71(13.48)	3] 0.014
		ADL	1] 29.48 (7.59) 2] 29.73 (7.88)		1] 29.30 (7.72) 2] 28.77 (8.24)	3] 0.105	1] 28.40 (7.97) 2] 27.23 (9.17)	3] 0.061
		NAI	1] 46.25 (6.44) 2] 46.62 (7.16)		1] 46.52 (6.36) 2] 45.19 (7.00)	3] 0.007	1] 6.40 (7.02) 2] 43.05 (9.12)	3] 0.003
		ZVT(1)	1] 204.09 (119.73) 2] 217.05 (111.54)		1] 198.72 (144.79) 2] 189.85 (110.92)	3] 0.141	1] 186.08 (124.78) 2] 173.14 (134.02)	3] 0.023
		ZVT(2)	1] 208.50 (139.69) 2] 210.61 (129.57)		1] 196.30 (142.64) 2] 189.29 (109.76)	3] 0.295	1] 196.53 (150.97) 2] 173.05 (119.22)	3] 0.071

EvTable168. Adverse Events: Cerebrolysin (CERE).

Adverse events (AE) identified in included studies	Bae, 2000	Panisset, 2002	Ruether, 1994	Ruether, 2001	Xiao, 1999	Xiao, 2000
Withdrawn (%) due to AE	T: 0 C: 0	T: 1 C: 0	T: 0 C: 0	T: 1 C: 1	T: 0 C: 0	T: NR C: NR
AE Checklist (Max 5)	5	4	5	4	3	2
None Reported	X		X			
Balance				X		
Accidental Injury		NS				
Dizziness		NS			NS	NS
Falls						
Behavioral						
Agitation					NS	
Cardiovascular		NS			NS	NS
Arrhythmia				X		
Hypotension					NS	NS
Hypertension					NS	NS
Extrapyramidal						
Tremor						NS
Gastrointestinal		NS				NS
Abdominal pain						
Constipation						
Diarrhea						
Dyspepsia						
Nausea, vomiting		NS		X		
Metabolic/nutritional						
Eating disorder						
Weight Change		S				
Neurological						
Asthenia		NS				
Psychiatric						
Anxiety		S				
Confusion, delirium						
Depression					NS	
Respiratory						
Cough, cold, infection				X		
Rhinitis				X		
Other		NS		X	NS	NS
Aberrant hematology		NS		NS		
Fatigue, weakness						
Fever, flu, pneumonia				X		
Headache		S		X		
Hepatic abnormality						
Muscle/joint disorder						
Pain		NS				
Rash, skin disorder					NS	
Sleep disorder					NS	NS
Urinary disorder						

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable169. Key characteristics: Estrogens.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Asthana 2001	PI	5	Placebo 17b-estradiol	NINCDS	AD	Probable Mild–Mod	20	20	80.0y (61-90y) 0%M	0.10 mg/d	8w	BMICT Boston Naming Test BPRS BSRT CIBIC DPRS FCMT IADL MMSE OMDR PSMS SCWIT Story Recall Trail-Making Test Treisman Visual Search Visual Paired-Associates	No
Henderson 2000	IF	6	Placebo Conjugated equine estrogens	NINCDS	AD	Probable Mild-Mod	42	36	78.0y (NR) 0%M	1.25 mg/d	16w	ADAS-Cog ADL CGIC CSGDS IADL MADRS Neuropsychological battery	No

EvTable169. Key characteristics: Estrogens cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Kyomen 1999 Auxiliary: Kyomen 2002	PI IS	8	Placebo Conjugated Equine Estrogens	DSM-III-R	Dementia	Mod-Sev	15	14	83.8y (>60y) 13%M 100% Institution	2.5 mg/d	4w	ABSR CSDD DSSS Katz ADL scale OAS (modified) TSI	No
Mulnard 2000	IF	7	Placebo Estrogen	NINCDS	AD	Probable Mild-Mod	120	97	75.0y (56-91y) 0%M	1.25mg/d	1y	ADAS-Cog ADCS-CGIC ADL ADL-BDRS Blessed-D CDRS Dependency Scale DST EFR HAM-D HDRS MAACLR MMSE NDT Neuropsychological Battery Trail-Making Test A	No

EvTable169. Key characteristics: Estrogens cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Wang 2000	IS PI	7	Placebo Premarin	NINCDS	AD	Mild-Mod	50	47	71.8y (NR) 0%M	1.25 mg/d	12w	BEHAVE-AD CASI (Chinese) CDR CIBIC+ HAM-D HDRS MMSE-CE HARS	No

EvTable170. Study results: Estradiol.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 8w	
Asthana 2001	OC Analysis 1] Placebo 2] Estradiol (17-β) 3] Placebo change over baseline 4] Estrogen change over baseline 5] Placebo vs estrogen in change from baseline	<u>SCWIT</u> <u>BSRT</u> FCMT CIBIC DPRS (mood) Functional Assessment (PSMS, IADL)					3] 110 (13)* 4] 90 (10)* 3] 7.0 (0.8)* 4] 8.2 (0.8)* 3] 22 (2.5)* 4] 26 (4.0)*	5] 0.02 5] 0.049 5] 0.03 5] 0.30 5] NS 5] NS

*SEM

EvTable171. Study results: Estrogen.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify) 4w		Final] (specify) 16w	
Henderson 2000	OC Analysis 1] Placebo 2] Estrogen (unopposed conjugated equine, Premarin) 3] Placebo change from baseline 4] Estrogen change from baseline 5] Placebo vs Estrogen change from baseline	ADAS-Cog CGIC ADL/IADL CSGDS MADRS			3] 1.2 (1.5) 4] -0.2 (1.1) 3] 3.8 (0.1) 4] 3.9 (0.1) 3] -1.1 (1.1) 4] 0.3 (0.8) 3] 1.2 (0.8) 4] 0.1 (1.2) 3] -2.0 (1.2) 4] -2.6 (1.3)	5] >0.1 5] >0.1 5] >0.1 5] >0.1 5] >0.1	3] 0.5 (1.7) 4] 1.8 (1.2) 3] 4.2 (0.1) 4] 4.2 (0.2) 3] 2.9 (1.5) 4] 2.9 (1.1) 3] -0.7 (1.2) 4] -1.4 (1.4) 3] 1.1 (1.4) 4] 0.2 (1.6)	5] >0.1 5] >0.1 5] >0.1 5] >0.1 5] >0.1

EvTable172. Study results: Estrogen.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify)		Final] (specify) 4w	
Kyomen 1999 Kyomen, 2002	OC Analysis 1] Placebo 2] Estrogen (conjugated equine) 3] Placebo change from baseline 4] Estrogen change from baseline 5] Placebo vs Estrogen in change from baseline	 ABSR CSDD KATZ ADL DSSS TSI	 1] 31.7 (9.0) 2] 31.6 (8.7)				 3] 4.74 (4.07) 4] 2.05 (1.73) 3] -2.17 (4.00) 4]- 3.75 (4.17) 3] 0.71 (1.71) 4] 0.41 (1.56) 1] 31.7 (9.0) 2] 19.6 (6.5) 3] 0.86 (3.24) 4] –0.71 (3.18)	 5] 0.03 5] 0.387 5] 0.677 3] <0.05 4] <0.03 5] 0.143

EvTable173. Study results: Estrogen.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12m	
Mulnard 2000	ITT Analysis 1] Placebo 2] Estrogen 3] Placebo change from baseline 4] Estrogen (0.625 mg/d) change from baseline 5] Estrogen (1.25 mg/d) change from baseline 6] Placebo (worsened %) 7] Estrogen (0.625mg/d, worsened %) 8] Estrogen(1.25 mg/d, worsened %)	<u>ADCS-CGIC</u> MMSE ADAS-Cog CDRS ADL-BDRS part 1 ADL-BDRS part 2 ADL-Dependency					3] 5.0 (1.1) 4] 5.1 (0.9) 5] 5.2 (0.9) 6] 74% 7] 80% 8] 80% 3] –3.1(4.1) 4] –2.7(3.5) 5] –2.7(3.9) 3] 3.6 (4.7) 4] 6.3 (8.7) 5] 4.8 (5.4) 3] 0.2 (0.4) 4] 0.4 (0.7) 5] 0.5 (0.6) 3] 1.2 (1.5) 4] 1.0 (1.2) 5] 1.0 (1.2) 3] 0.8 (1.6) 4] 1.0 (1.4) 5] 0.92 (1.4) 3] 0.4 (1.1) 4] 0.4 (0.8)	9] 0.46 10] 0.36 11] 0.73 12] 0.73 9] 0.48 10] 0.64 9] 0.09 10] 0.32 9] 0.03 10] 0.01 9] 0.80 10] 0.61 9] 0.56 10] 0.73 9] 0.59 10] 0.21

EvTable173. Study results: Estrogen cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify)		Final: (specify) 12m	
		9] Placebo vs estrogen 0.65mg/d change from baseline 10] Placebo vs estrogen 1.25mg/d change from baseline 11] Placebo vs estrogen .065mg/d % worse 12] Difference between Place and estrogen 1.25mg/d % worse	Score Mood scores(HDRS) Memory scores (EFR) Memory scores (NDT) Attention scores (letter cancellation) Attention scores Trail-making test-A Attention scores DST Language scores (category fluency) Language scores (letter fluency)					5] 0.5 (1.0) 3] 0.03 (3.9) 4] 0.5 (3.7) 5] –1.1 (4.3) 3] –5.7 (22.4) 4]-11.1 (15.2) 5] –8.2 (13.2) 3] –0.9 (3.1) 4] –0.9 (3.5) 5] –2.1 (2.6) 3] –1.3 (5.5) 4] –0.6 (8.7) 5] –2.3 (6.0) 3] 18.6 (43.4) 4] 19.0 (54.2) 5] 18.8 (42.8) 3] –3.9 (6.8) 4] –2.4 (6.8) 5] –4.5 (8.5) 3] –2.9 (6.6) 4] –6.3 (9.0) 5] –5.0 (5.7) 3] –1.7 (6.8) 4] –3.1 (5.8)	 9] 0.69 10] 0.69 9] 0.08 10] 0.41 9] 0.57 10] 0.19 9] 0.90 10] 0.45 9] 0.89 10] 0.98 9] 0.47 10] 0.99 9] 0.06 10] 0.13 9] 0.32 10] 0.71

EvTable173. Study results: Estrogen cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify)		Final: (specify) 12m	
			Motor scores (Grooved Pegboard Test) Motor scores(Finger Tapping Test)					5] –2.1 (7.1) 3] -5.2 (42.4) 4] –0.6 (2.7) 5] –5.9 (5.5) 3] 4.0 (9.6) 4] –1.3 (10.2) 5] 1.7 (6.9)	9] 0.90 10] 0.86 9] 0.04 10] 0.25

EvTable174. Study results: Estrogen.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point] (specify) 6w		Final] (specify)12w	
Wang 2000	ITT Analysis 1] Placebo 2] Estrogen (Conjugated, Premarin) 3] Placebo change from baseline 4] Estrogen change from baseline 5] Placebo vs Estrogen in change from baseline	CASI-Total CDR CIBIC+ BEHAVE-AD HARS HDRS			3] -0.7 (8.2) 4] 0.4 (5.2) 3] 0.0 (0.4) 4] 0.0 (0.3) 3] -0.2 (0.8) 4] -0.2 (0.9)	5] NS 5] NS 5] NS	3] 0.5 (8.2) 4] 1.0 (8.0) 3] 0.1 (0.4) 4] 0.0 ±0.4 3] -0.2 (0.8) 4] -0.2 (1.0) 3] -0.8 (5.0) 4] -0.4 (3.8) 3] 0.4 (2.6) 4] -0.8 (4.7) 3] 0.4 (4.8) 4] -1.2 (5.8)	5] NS 5] NS 5] NS 5] NS 5] NS

EvTable175. Adverse Events: Estrogens.

Adverse events (AE) identified in included studies	Asthana, 2001	Henderson, 2000	Kyomen, 1999	Mulnard, 2000	Wang, 2000
Withdrawn (%) due to AE	T: 0 C: 0	T: 5 C: 5	T: 0 C: 0	T: 14 C: 5	T: 4 C: 0
AE Checklist (Max 5)	1	3	5	3	2
None Reported			x		
Balance					
Accidental Injury					
Dizziness					
Falls				NS	
Behavioral					
Agitation					
Cardiovascular					
Arrhythmia					
Hypotension					
Hypertension					NS
Extrapyramidal					
Tremor					
Gastrointestinal					
Abdominal pain					
Constipation					
Diarrhea					
Dyspepsia					
Nausea, vomiting					NS
Metabolic/nutritional					
Eating disorder					
Weight Change					
Neurological					
Asthenia					
Psychiatric				NS	
Anxiety					
Confusion, delirium					
Depression					
Respiratory					
Cough, cold, infection					
Rhinitis					
Other	x	x		NS	S
Aberrant hematology					
Fatigue, weakness					
Fever, flu, pneumonia					
Headache					NS
Hepatic abnormality					
Muscle/joint disorder					
Pain					
Rash, skin disorder	x				NS
Sleep disorder					
Urinary disorder					

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable176. Key characteristics: Gingko Biloba.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	#Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Kanowski 1996	PI	8	Placebo Ginkgo Biloba (EGb 761)	DSM-III-R	DAT MID	Mild-Mod	216	156	69.6y (≥55y) 33%M 100% Community	240 mg/d	24w	CGI NAB MADRS SKT	DAT vs MID
Le Bars 1997 Auxiliary: Le Bars 2002 Le Bars 2000 Pors 1998	IF	8	Placebo Ginkgo Biloba	DSM-III-R ICD-10	AD MID	Mild-Modly Sev	327	137	69.0y (45-90y) 46%M	40 mg tid	52w	ADAS-Cog CGIC GERRI	AD vs MID+AD MMSE
Maurer 1997	NR	6	Ginkgo Biloba (Egb761)	DSM-III-R NINCDS	DAT PDD	Mild-Mod	20	18	64.6y (50-80y) 50%M	240 mg/d	3m	ADAS-Cog ADAS-Noncog CGI EEG SKT Trail Making	No

EvTable177. Study results: Ginkgo Biloba (EGb761).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 24w**	
Kanowski 1996	ITT Analysis 1] Placebo 2] Ginkgo Biloba (EGb761) 240 mg/d 3] Placebo probable MID 4] Ginkgo Biloba probable MID 5] Placebo probable DAT 6] Ginkgo Biloba probable DAT 7] Placebo vs. Ginkgo Biloba change from baseline	SKT NAB CGI(numbers improved compared with baseline) MADRS	1] 11.2 (3.4) 2] 10.2 (3.0) 3] 12.2 (3.3) 4] 10.9 (3.7) 5] 11.0 (3.4) 6]10.2 (2.8) 1] 21.1 (3.7) 2] 21.0 (3.6) 3] 23.3 (4.0) 4] 21.2 (3.3) 5] 20.7 (3.5) 6] 21.0 (3.7) 3] 4.8 (0.4) 4] 4.9 (1.0) 5] 4.9 (0.4) 6] 5.0 (0.4) 1] 16.1 (7.2) 2] 16.5 (6.8)				1] 10.4 (4.9) 2] 8.0 (4.3) 3] 11.8 (3.9) 4] 9.4 (4.4) 5] 10.1 (5.0) 6] 7.6 (4.2) 1] 20.5 (3.6) 2] 20.1 (3.6) 3] 22.3 (3.9) 4] 20.6 (3.3) 5] 20.2 (3.5) 6] 19.9 (3.7) 1] 42/77 2] 57/79 3] 3.8 (1.0) 4] 3.7 (0.8) 5] 4.6 (1.0) 6] 4.0 (0.8) 1] 13.6 (7.3) 2] 13.2 (6.5)	7] <0.05 7] <0.10 7] <0.05 7] NS

EvTable178. Study results: Ginkgo Biloba (EGb761).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 52w	
Le Bars 1997 Le Bars 2002 Le Bars 2000 Por 1998	ITT Analysis 1] Placebo change from baseline AD & MID 2] Ginkgo Biloba (EGb761) 40 mg tid change from baseline AD & MID 3] Placebo change from baseline AD only 4] Ginkgo Biloba (EGb761) 40 mg tid change from baseline AD only 5] Placebo vs Ginkgo Biloba in change from baseline AD & MID 6] Placebo vs Ginkgo Biloba in change from baseline AD only	ADAS-Cog GERRI CGIC (Rating mean)					1] 1.5 CI (0.4 to2.5) 2] 0.1 CI (-1.8 to1.0) 3] 1.5 CI (0.3 to 2.6) 4] –0.2 CI (-1.2 to 0.8) 1] 0.08 CI (0.01 to 0.14) 2]-0.06 CI(-0.13 to 0.01) 3] 0.09 CI (0.02 to 0.17) 4] –0.09 CI (-0.16 to -0.02) 1] 4.2 CI (4.1-4.3) 2] 4.2 CI (4.1-4.4) 3] 4.2 CI (4.1 to 4.4) 4] 4.2 CI (4.1 to 4.4)	5] 0.04 6] 0.02 5] 0.004 6] <0.001 5] 0.77 6] 0.21

EvTable179. Study results: Ginkgo Biloba (EGb761, Tebonin forte).

Author Year	Analysis Groups	Outcome Measures	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 3m	
Maurer 1997	SKT: ITT Analysis Others: OC Analysis 1] Placebo 2] Ginkgo Biloba (EGb761, Tebonin forte) 240 mg/d 3] Difference between placebo and Ginkgo Biloba in change from baseline 4] Difference between placebo and Ginkgo Biloba in numbers improved	<u>SKT</u> ADAS-Cog CGI (numbers improved compared with baseline)	1] 18.11 (9.43) 2] 19.67 (6.31) 1]36.10(15.23) 2]31.21(12.63)				1]18.89(9.13) 2]16.78(6.87) 1]36.13(15.56) 2]30.33(14.77) 1] 1/9 2] 5/9	3] <0.013 3] NS 4] 0.069

EvTable180. Adverse Events: Gingko Biloba.

Adverse events (AE) identified in included studies	Kanowski, 1996	Le Bars, 1997	Maurer, 1997
Withdrawn (%) due to AE	T: 0 C: 0	T: 6 C: 6	T: 0 C: 0
AE Checklist (Max 5)	4	3	5
None Reported		x	x
Balance			
Accidental Injury			
Dizziness			
Falls			
Behavioral			
Agitation			
Cardiovascular			
Arrhythmia			
Hypotension			
Hypertension			
Extrapyramidal			
Tremor			
Gastrointestinal	x		
Abdominal pain			
Constipation			
Diarrhea			
Dyspepsia			
Nausea, vomiting			
Metabolic/nutritional			
Eating disorder			
Weight Change			
Neurological			
Asthenia			
Psychiatric			
Anxiety			
Confusion, delirium			
Depression			
Respiratory			
Cough, cold, infection			
Rhinitis			
Other			
Aberrant hematology			
Fatigue, weakness			
Fever, flu, pneumonia			
Headache	x		
Hepatic abnormality			
Muscle/joint disorder			
Pain			
Rash, skin disorder	S		
Sleep disorder			
Urinary disorder			

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable181. Key characteristics: Idebenone.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Bergamasco 1994	NR	6	Placebo Idebenone	DSM III NINCDS	DAT	Mild – Modly Sev Probable	92	83	70.0y (55-80y) 47%M	30 mg tid	90d	BDRS GBS Laboratory tests Rey's 15 Word Test Rey's A Figure Test SCAG Token Test Word Fluency Test	No
Gutzmann 1998 Auxiliary: Weyer 1996	NR	6	Placebo Idebenone	DSM-III-R NINCDS	AD PDD	Mild-Modly Sev	450	379	69.9y (58-82y) 34%M	120 mg tid	12m	ADAS (Cog/NODCOS) Adverse Events Caregiver observation CGI Laboratory tests ECG IADL NOSGER SKT	Disease severity
Gutzmann 2002	PI	7	Idebenone Tacrine	NINCDS DSM-III-R	AD PDD	Mild-Mod	203	44	71.2y (44-90y) 36%M 100% White 100% Community	360 mg/d 160 mg/d	60w	ADAS-Cog ADAS-Noncog ADAS-Total CGI CT EIS HIS MRI NOSGER-IADL	No

EvTable181. Key characteristics. Idebenone cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Marigliano 1992	NR	7	Placebo Idebenone	DSM-III-R	MID	Mild-Mod	108	108	73.6y (65-80y) 49%M 31% Institution 69% Community	45 mg bid	120d	ECG GBS HIS HRSD Laboratory tests MMSE Randt Memory Test Token Test TP	No
Weyer 1997	NR	5	Placebo Idebenone	DSM-III-R NINCDS	PDD DAT	Mild-Mod	300	247	70.0y (54-90y) 34%M	30 mg/d 90 mg/d	6m	ADAS- Total ADAS-Cog ADAS-Noncog CGI DSS Greene's Assessment HAMD MMSE NAA NAB Laboratory tests	Disease severity

EvTable182. Study results: Idebenone.

Author Year	Outcomes Measured	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 45d**		**Final: (specify) 90d**	
Bergamasco 1994	OC Analysis 1] Placebo 2] Idebenone 30 mg tid 3] Placebo difference from baseline 4] Idebenone difference from baseline 5] Idebenone vs Placebo change from baseline	SCAG total score Rey's 15 Word Test TK BDRS	1] 60.00(2.02)* 2] 57.10(1.99)* 1] 14.07(0.91)* 2] 17.31(1.41)* 1] 22.84(0.82)* 2] 23.80(0.89)* 1] 17.07(1.01)* 2] 17.50(1.22)*		1] 59.20(1.64)* 2] 55.24(1.75)* 1] 14.95(0.87)* 2] 20.14(1.64)* 1] 22.79(0.83)* 2] 24.48(0.92)* 1] 16.83(1.06)* 2] 18.12(1.23)*	4] <0.05 4] <0.05 4] <0.05	1] 57.62(1.70)* 2] 53.00(2.18)* 1] 15.24(1.02)* 2] 21.28(1.78)* 1] 23.22(0.81)* 2] 24.68(0.89)* 1] 16.03(1.18)* 2] 19.17(1.37)*	4] <0.05 5] <0.05 4] <0.05 5] NS 3] <0.05 4] <0.05 5] <0.05

*SEM

EvTable183. Study results: Idebenone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6m**		**Final: (specify) 12m**	
Gutzman, 1998 Weyer, 1996	ITT Analysis 1] Placebo 90mg 2] Idebenone 90 mg tid 3] Idebenone 120 mg tid 4] Placebo change from baseline 5] Idebenone 90 mg tid change from baseline 6] Idebenone 120 mg tid change from baseline 7] Dose trend	<u>ADAS Total</u> ADAS-Cog CGI NOSGER-IADL	1] 34.3 (9.3) 2] 35.3 (9.3) 3] 32.7 (8.0) 1] 5.2 (0.4) 2] 5.2 (0.5) 3] 5.1 (0.4) 1] 16.0 (4.8) 2] 16.0 (4.9) 3] 15.3 (4.9)		4] --5.6 (8.2) 5] -7.2 (7.4) 6] -8.4 (8.1) 4] -3.4 5] -4.9 6] -6.0	7] <0.0027 7] <0.001	4] -4.9 (8.5) 5] -7.1 (8.6) 6] -8.8 (9.5) 4] -3.0 5] -5.0 6] -7.0 1] 63.3 2] 73.4 3] 87.3 1] 36.7 2] 41.1 3] 48.4	7] 0.0001 7] <0.0005 7] 0.0000 7] 0.0298

EvTable184. Study results: Idebenone-Tacrine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 60 w**	
Gutzmann 2002	ITT Analysis 1] Idebenone 360 mg d 2] Tacrine 160 mg d variable 3] Difference between Idebenone and Tacrine	EIS% Rating = -1 Rating = 0 Rating = 1 Rating = 2 Rating = 3 ADAS-Total ADAS-Cog ADAS-Noncog CGI-S NOSGER-IADL	 1] 41.55(16.46) 2] 41.52(14.92) 1] 30.23(11.59) 2] 30.93(10.59) 1] 11.32 (6.79) 2] 10.55(5.86) 1] 5.22 (0.46) 2] 5.19 (0.44) 1] 13.88(4.43) 2] 13.78(4.55)				1] 28.9% 2] 9.0% 1] 54.8% 2] 83.8% 1] 16.3% 2] 7.1% 1] 13.5% 2] 3.0% 1] 8.7% 2] 4.0% 1] 6.7% 2] 2.0% 1] 34.51(17.43) 2] 30.44(16.32) 1] 26.40(16.67) 2] 24.81(14.92) 1] 8.11(7.56) 2] 5.63(6.10) 1] 4.43 (1.58) 2] 4.53 (1.45) 1] 13.13 (5.49) 2] 12.5 (6.25)	 3] <0.0001 favours Idebenone 3] NS 3] NS 3] NS

EvTable185. Study results: Idebenone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 60d**		**Final: (specify) 150d**	
Marigliano 1992	OC Analysis 1] Placebo 2] Idebenone 45 mg bid 3] Placebo change from baseline 4] Idebenone 45 mg bid change from baseline 5] Idebenone 45 mg bid vs. placebo	RMT-Delayed Recall RMT-Figure Recognition RMT Paired Word-Acquisition GBS Intellectual Functions GBS Motor functions	1] 62 2] 60 1] 7 2] 6.5 1] 6 2] 5.5 1] 16.5 2] 16.5 1] 7 2] 7		1] 59 2] 64 1] 6 2] 6.4 1] 6 2] 5 1] 16 2] 15 1] 7 2] 6	4] <0.04 5] <0.05	1] 55 2] 61 1] 5.5 2] 6.5 1] 2.5 2] 6 1] 13 2] 11 1] 4.5 2] 5	5] <0.02 5] <0.02 5] <0.02 5] <0.05

EvTable186. Study results: Idebenone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3m**		**Final: (specify) 6m**	
Weyer, 1997	ITT Analysis							
	1] Placebo change from baseline	ADAS-Total			1] -1.6		1] -5.7	7] 0.037
					2] -5		2] -5.6	8] 0.009
					3] -6.9		3] -8.0	
					4] -6.1		4] -7.0	
					5] -6.5		5] -7.6	
	2] Idebenone 30 mg tid change from baseline				6] -9.5		6] -11.1	
		ADAS-Cog						
					1] -3.6		1] -4.5	7] 0.031
					2] -3.8		2] -4.4	8] 0.006
	3] Idebenone 90 mg tid change from baseline				3] -5.5		3] -6.5	
					4] -4.8		4] -5.8	
					5] -5.0		5] -5.9	
					6] -7.3		6] -8.9	
		ADAS-Noncog						
	4] Placebo ADAS-Total >20 change from baseline				1] -0.9		1] -1.2	7] 0.035
					2] -1.3		2] -1.9	8] 0.014
					3] -1.3		3] -2.0	
					4] -1.5		4] -1.8	
					5] -1.6		5] -2.2	
	5] Idebenone30 ADAS-Total >20 change from baseline				6] -2.3		6] -3.2	
		CGI % improved						
							1] 67.5	7] 0.018
							2] 72.2	8] 0.000
	6] Idebenone 90 ADAS-Total >20 change from baseline						3] 81.6	
							4] 47.9	
							5] 66.7	
							6] 88.5	
	7] Treatment effect 0 to 6m							
	8] Treatment effect 0 to 6m sub-group ADAS-Cog >20							

EvTable187. Adverse Events: Idebenone.

Adverse events (AE) identified in included studies	Bergamasco, 1994	Gutzmann, 1998	Marigliano, 1992	Weyer, 1997	IDEBENONE(C) TACRINE (T) Gutzmann, 2002
Withdrawn (%) due to AE	T: 4 C: 2	T: NR C: NR	T: 0 C: 0	T: 5 C: 5	T: 41 C: 17
AE Checklist (Max 5)	4	1	5	3	3
None Reported					
Balance			x		
Accidental Injury					
Dizziness		x		NS*	
Falls			x		
Behavioral	x				
Agitation					
Cardiovascular				x	
Arrhythmia			x		
Hypotension		NS*			
Hypertension					
Extrapyramidal					
Tremor					
Gastrointestinal			x		S*
Abdominal pain	x				
Constipation					
Diarrhea					
Dyspepsia				x	
Nausea, vomiting	x			x	S*
Metabolic/nutritional					
Eating disorder					
Weight Change					
Neurological		NS*			
Asthenia					
Psychiatric					
Anxiety	x				
Confusion, delirium			x		
Depression					
Respiratory		x		NS*	
Cough, cold, infection					
Rhinitis					
Other			x		
Aberrant hematology		NS*			
Fatigue, weakness					
Fever, flu, pneumonia		x			
Headache				x	
Hepatic abnormality				NS*	S*
Muscle/joint disorder					
Pain		x			
Rash, skin disorder			x		
Sleep disorder	x				
Urinary disorder					

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable188. Key characteristics: Oxiracetam.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Bottini 1992	PI	6	Placebo Oxiracetam	DSM III NINCDS	PDD MID Mixed	NR	65	58	71.0y (54-82y) 43%M	800 mg bid	12w	DSPT QoL RPM RT TK WLM Verbal Fluency Short Story	No
Maina 1989	NR	6	Placebo Oxiracetam	DSM III	PDD MID MIXED	NR	289	272	73.0y (<85y) 50%M	800 mg bid	12w	BDS Global Evaluation of efficacy IPSE-E NMICS IPAX-E AE	PDD vs MID
Mangoni 1988	PI	6	Placebo Oxiracetam	NINCDS	AD	Probable-Possible Mild-Mod	30	30	62.0y (52-79y) 67%M	800 mg bid	24w	IPSC-E LNNB Sensory motor left scale Frontal right scale	No

EvTable188. Key characteristics: Oxiracetam cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	#Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Rozzini 1992 Auxiliary: Rozzini 1993	NR	4	Placebo Oxiracetam	DSM-III-R	PDD	Mild-Mod	110	94	73.8y (>65y) 34%M	800 mg bid	26w	AMI BI BDI BMDI IADL MMSE RT	No
Villardita 1992	PI	6	Placebo Oxiracetam	NINCDS DSM III	AD MID	Mild-Mod	60	60	69.8y (52-83y) 60%M	800 mg bid	90d	ACPT BTT DS IADL-E IPSC-E LAS MMSE MWF Rosy's WT	No

EvTable189. Study results: Oxiracetem.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 6w		Final: (specify) 12w	
Bottini 1992	Completer Analysis 1] Placebo 2] Oxiracetem 800 mg bid 3] Placebo vs baseline 4] Oxiracetem vs baseline 5] Oxiracetem vs Placebo	Reaction Time milli second Verbal Fluency phonemic Verbal Fluency semantic Short Story RPM DSPT WLM TK Italian QoL	1] 783 (634) 2] 1018 (873) 1] 12.6 (8.21) 2] 13.3(12.37) 1] 13.8 (13.0) 2] 12.9 (7.31) 1] 7.8 (12.54) 2] 5.2 (6.24) 1] 13.9 (7.34) 2] 13.1 (6.15) 1] 4.3 (0.94) 2] 4.2 (0.95) 1] 4.0 (3.71) 2] 3.6 (2.98) 1] 22.6 (5.83) 2] 23.3 (6.11) 1] 2.7 (0.55) 2] 2.8 (0.56)		1] 2.7 (0.54) 2] 3.1 (0.53)		1] 697 (350) 2] 996 (1101) 1] 9.8 (7.74) 2] 14.2 (10.2) 1] 13.0 (7.02) 2] 14.7 (7.31) 1] 6.1 (5.942) 2] 9.7 (11.67) 1] 12.7 (6.08) 2] 14.5 (6.5) 1] 4.5 (1.03) 2] 4.7 (1.16) 1] 4.7 (3.97) 2] 5.1 (3.73 1] 23.8 (6.16) 2] 23.1 (7.17) 1] 2.5 (0.62) 2] 3.2 (0.50)	5] NS 5] 0.009 5] <0.02 5] 0.02 5] 0.007 3] <0.01 4] <0.01 5] NS 3] <0.01 4] <0.01 5] <0.05 5] NS 5] <0.001

EvTable190. Study results: Oxiracetem.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Maina, 1989	Per Protocol Analysis 1] Placebo 2] Oxiracetem 800 mg bid 3] Difference between treatments in favor of Oxiracetem 4] Time by treatment interaction	BDS NMICS IPSE-E Global evaluation of efficacy	1] 10.5 (4.20) 2] 10.7 (4.25) 1] 17.3 (7.06) 2] 18.4 (7.34) 1] 1.9 (0.35) 2] 2.0 (0.34)	3] NS			1] 10.3 (4.54) 2] 9.0 (4.17) 1] 17.7 (20.9) 2] 20.9 (6.93) 1] 1.8 (est) 2] 1.51 (est) Good or very good 1] 21% 2] 64%	3] <0.01 3] <0.01 4] <0.01 3] <0.01 3] <0.01

EvTable191. Study results: Oxiracetem.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12w**		**Final: (specify) 24w**	
Mangoni 1998	Completer Analysis 1] Placebo 2] Oxiracetem 800 bid 3] Between treatment in favor of Oxiracetem 4] Time by treatment interaction	IPSC-E LNNB Sensory-motor left scale Frontal right scale	1] 2.1 (0.75) 2] 2.3 (0.68)	3] NS	1] 1.94 (est) 2] 1.67 (est)		1] 2.1 (est) 2] 1.75 (est) 3] 7/14 tests 4] 7/14 tests	3] <0.01 4] <0.001 3] <0.01 4] <0.01 4] <0.01 4] <0.01

EvTable192. Study results: Oxiracetem.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 2m**		**Final: (specify) 6m**	
Rozzini, 1992 Rozzini 1993	OC Analysis 1] Placebo 2] Oxiracetem 800 mg bid 3] Oxiracetem vs baseline 4] Placebo vs. Oxiracetam change from baseline	BI IADL MMSE RT score BDI Test of Attention Matrix	1] 94.89 (9.79) 2] 94.38(10.69) 1] 1.52 (1.64) 2] 1.48 (1.62) 1] 21.98 (2.77) 2] 22.08 (2.78) 1] 1.84 (1.95) 2] 8.67 (2.05) 1] 20.43(14.49) 2] 23.79(17.96) 1] 18.83 (8.72) 2] 18.46 (9.14)		1] 94.67(10.02) 2] 94.17(10.77) 1] 1.57(1.70) 2] 1.50 (1.72) 1] 22.22(3.01) 2] 23.35(3.18) 1] 8.84 (1.79) 2] 7.64 (2.47) 1] 21.04(15.92) 2] 20.75(16.21) 1] 19.39 (7.21) 2] 19.27 (8.96)	 3] <0.05 3] <0.05 3] NS	1] 94.46(10.28) 2] 93.96(11.32) 1] 1.63 (1.85) 2] 1.56 (1.73) 1] 22.04(3.28) 2] 22.71 (3.58 1] 8.85(2.04) 2] 7.54(2.44) 1] 22.25(16.82) 2] 23.58(16.4) 1]18.85 (6.92) 2] 20.31 (8.92)	4] NS 3] NS 4] NS 3] <0.02 3] NS

EvTable193. Study results: Oxiracetem.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 90d	
Villardita 1992	OC Analysis 1] Placebo 2] Oxiracetem 800 mg bid 3] Placebo vs baseline 4] Oxiracetem vs baseline 5] Oxiracetem vs Placebo	MMSE ACPT R15WT immediate R15WT delayed DS forward DS backward IPSC-E total IADL-E total	1] 16.7 (0.8)* 2] 15.5 (0.9)* 1] 18.5 (0.8)* 2] 17.2 (0.9)* 1] 18.8 (1.1)* 2] 18.5 (1.1)* 1] 2.4 (0.3)* 2] 2.3 (0.3)* 1] 4.5 (0.3)* 2] 4.5 (0.2)* 1] 3.1 (0.2)* 2] 3.0 (0.2)* 1] 152.7 (4.1)* 2] 149.9(4.4)* 1] 20.9(1.2)*				1] 15.6 (0.8)* 2] 21.6 (1.0)* 1] 17.3 (1.0)* 2] 21.6 (1.0)* 1] 18.4 (1.1)* 2] 20.6 (1.1)* 1] 2.5 (0.2)* 2] 2.8(0.2)* 1] 4.1 (0.2)* 2] 4.5 (0.2)* 1] 3.1 (0.2)* 2] 2.9 (0.2)* 1] 155.9 (4.2)* 2] 157.6 (5.2)* 1] 19.6 (1.0)* 2] 26.0 (1.0)*	3] NS 4] <0.01 5] <0.01 3] NS 4] <0.05 5] <0.05 3] NS 4] <0.05 5] <0.05 3] NS 4] <0.05 5] NS 5] NS 5] NS 5] NS 3] <0.05 4] <0.01 5] <0.01

*SEM

EvTable194. Adverse Events: Oxiracetam.

Adverse events (AE) identified in included studies	Bottini, 1992	Maina, 1989	Mangoni, 1988	Rozzini, 1992	Villardita, 1992
Withdrawn (%) due to AE	T: 6 C: 0	T: 2 C: 2	T: 0 C: 0	T: 4 C: 9	T: 0 C: 0
AE Checklist (Max 5)	4	5	5	2	5
None Reported			x		
Balance					
Accidental Injury					
Dizziness	x				
Falls					
Behavioral					
Agitation		x			
Cardiovascular					
Arrhythmia					
Hypotension					
Hypertension					
Extrapyramidal	x				
Tremor					
Gastrointestinal				x	
Abdominal pain	x	x		x	
Constipation		x			
Diarrhea					
Dyspepsia				x	
Nausea, vomiting					
Metabolic/nutritional					
Eating disorder	x				
Weight Change					
Neurological					
Asthenia					
Psychiatric					
Anxiety				x	x
Confusion, delirium		x			
Depression					
Respiratory					
Cough, cold, infection					
Rhinitis					
Other	x				
Aberrant hematology		NS			
Fatigue, weakness					
Fever, flu, pneumonia					
Headache					
Hepatic abnormality					
Muscle/joint disorder					
Pain					
Rash, skin disorder	x				
Sleep disorder	x				x
Urinary disorder	x				

NR = Withdrawals due to AE Not Reported + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable195. Key characteristics. Pentoxifylline.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Knezevic 1996	IF	6	Placebo Pentoxifylline	DSM-III-R	MID	Mild-Mod	289	239	69.7y (45-90y) 56%M	1200 mg/d	9m	GBS MMSE Neuropsychological SCAG	No
Black 1992	PI	6	Placebo Pentoxifylline	DSM III	MID	Nild-Mod	64	38	75.4y (55-98y) 52%M	400 mg tid	36w	ADAS-Cog ADAS-Noncog HIS MMSE	Vascular change vs Discrete strokes
Ghose 1987	IF	6	Placebo Pentoxifylline	DSM III	PDD MID	Mild-Mod	36	28	77.0y (60-88y) 50%M	400 mg tid	12w	Digit Span Test DSPT MMSE RT SCAG Shopping list	MID vs PDD
DRUG VS DRUG													
Parnetti 1997	NR	5	Sulodexide Pentoxifylline	NINDS-AIREN	VaD	Probable Mild-Mod	93	86	75.0y (65-80y) 40%M	100 mg/d 1200 mg/d	6m	GBS Laboratory tests MMSE	No

EvTable196. Study results: Pentoxifylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 9m**	
Knezevic, 1996	ITT/LOCF Analysis 1] Placebo 2] Pentoxifylline 1200 mg/day 3] Placebo change from baseline 4] Pentoxifylline change from baseline 5] Placebo vs Pentoxifylline change from baseline	<u>GBS total</u> GBS Intellectual GBS Motor GBS emotional MMSE SCAG Total SCAG cognitive	1] 37.2 (17.2) 2] 37.9 (17.5) 1] 43.9 (11.8) 2] 44.8 (11.7)				3] 0.0 (13.9) 4] -2.1 (14.7) 3] 0.0 (7.0) 4] –0.9 (7.6) 3] 0.2 (5.0) 4] 0.0 (9.5) 3] 0.3 (2.3) 4] –0.3 (2.8) 3] –1.9 (9.0) 4] –3.1 (10.4) 3] –0.4 (3.5) 4] –1.3 (3.6)	5] 0.065 5] 0.060 5] 0.275 5] 0.072 5] NS 5] 0.034 5] 0.007

EvTable197. Study results: Pentoxifylline.

Author Year	Analysis Groups	Outcome Measures	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 36w**	
Black 1992	Efficacy Analysis 1] Placebo 2] Pentoxifylline 1200 mg/d 3] Pentoxifylline Placebo change from baseline 4] Placebo Subgroup with vascular damage 5] Pentoxifylline subgroup with vascular damage 6] Placebo vs Pentoxfylline change from baseline subgroup with vascular damage 7] Placebo subgroup with discrete strokes 8] Pentoxifylline subgroup with discrete strokes 9] Placebo vs Pentoxifylline change from baseline subgroup with discrete strokes	<u>ADAS-total</u> ADAS-Cog ADAS-Noncog ADAS without cognitive memory	1] 30.08 2] 26.5 4] 29.17 5] 22.94 7] 30.77 8] 26.72 1] 25.39 2] 21.69 4] 24.81 5] 18.34 7] 25.72 8] 21.72 1] 4.69 2] 4.81 4] 4.36 5] 4.60 7] 5.05 8] 5.00 1] 7.78 2] 6.63 4] 7.20 5] 5.07 7] 7.78 8] 6.00				1] 37.03 2] 28.19 4] 34.98 5] 20.85 7] 41.99 8] 25.36 1] 30.41 2] 23.10 4] 28.83 5] 17.11 7] 33.24 8] 21.14 1] 6.63 2] 5.09 4] 6.16 5] 3.73 7] 8.73 8] 4.22 1] 10.16 2] 6.72 4] 8.96 5] 3.47 7] 12.84 8] 5.28	3] 0.058 6] 0.023 9] 0.002 3] 0.064 6] 0.020 9] 0.005 3] 0.23 6] 0.12 9] 0.017 3] 0.036 6] 0.005 9] 0.001

EvTable198. Study results: Oxpentifylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Ghose, 1987	Per protocol analysis 1] Placebo PDD 2] Placebo MID 3] Oxpentifylline 400 mg tid PDD 4] Oxpentifylline 400 mg tid MID 5] Placebo all 6] Oxpentifylline all 7] Oxpentifylline vs Placebo MID 8] Oxpentifylline vs Placebo PDD	<u>MMSE</u> <u>SCAG</u> DSST	1] 19.4 2] 19.6 3] 16.6 4] 16.5 5] 19.9 6] 16.6 1] 42.1 (14.3) 2] 44.1 (16.3) 3] 53.5 (15.6) 4] 43.0 (16.7) 5] 42.1 (14.3) 6] 50 (16) 5] 5.5 (1.4) 6] 5.4 (1.3)				1] 20.4 2] 21.3 3] 18.3 4] 20.3 5] 21.3 6] 19.5 1] 37.3 (14.0) 2] 39.9 (14.8) 3] 44.3 (13.0) 4] 41.0 (10.4) 5] 37.4 (14.4) 6] 43.51 (12.9) 5] 6.2 (1.4) 6] 5.7 (1.2)	7] <0.05 8] NS 7] NS 8] NS 7] NS 8] NS

EvTable199. Study results: Sulodexide - Pentoxifylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 4m**		**Final: (specify) 6m**	
Parnetti, 1997	OC Analysis 1] Sulodexide 50 mg bid 2] Pentoxifylline 400 mg tid 3] sulodexide change vs baseline	GBS motor impairment GBS intellectual impairment GBS emotional impairmen MMSE	1] 1.64 (0.14)* 2] 1.59 (0.13)* 1] 2.09 (0.09)* 2] 1.98 (0.08)* 1] 2.1 (0.12)* 2] 1.89 (0.1)* 1] 17.6 (0.4)* 2] 18 (0.4)*		1] 1.58 (0.14)* 2] 1.53 (0.14)* 1] 1.88 (0.09)* 2] 1.95 (0.1)* 1] 1.88 (0.12)* 2] 1.9 (0.1)*	3] <0.01 3] <0.01 3] <0.12	1] 1.54 (0.16)* 2] 1.46 (0.17)* 1] 1.79 (0.1)* 2] 1.87 (0.12)* 1] 1.76 (0.12)* 2] 1.75 (0.11)* 1] 20 (0.6)* 2] 20 (0.4)*	3] <0.01 3] <0.01 3] <0.01

*SEM

EvTable200. Adverse Events. Pentoxifylline.

Adverse events (AE) identified in included studies	Black, 1992	Ghose, 1987	Knezivic, 1996	PENTOXIFYLLINE SULODEXIDE Parnetti, 1997
Withdrawn (%) due to AE	T: 22 C: 25	T: 12 C: 6	T: 0 C: 0	T: 7 C: 6
AE Checklist (Max 5)	1	2	3	2
None Reported			X	
Balance				
Accidental Injury				
Dizziness				
Falls				
Behavioral				
Agitation				
Cardiovascular	X			X
Arrhythmia				
Hypotension				
Hypertension				
Extrapyramidal				
Tremor				
Gastrointestinal	X	X		
Abdominal pain				X
Constipation				
Diarrhea				
Dyspepsia				
Nausea, vomiting	X	X		
Metabolic/nutritional				
Eating disorder				
Weight Change				
Neurological	X			
Asthenia				X
Psychiatric				
Anxiety				
Confusion, delirium				
Depression				
Respiratory				
Cough, cold, infection				
Rhinitis				
Other				
Aberrant hematology				
Fatigue, weakness				
Fever, flu, pneumonia				
Headache				X
Hepatic abnormality				
Muscle/joint disorder				
Pain				
Rash, skin disorder				
Sleep disorder				
Urinary disorder				

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable201. Key characteristics: Propentofylline.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Marcusson 1997	NR	5	Placebo Propentofylline	DSM-III-R	AD VaD	Mild-Mod	260	187	72.4y (NR) %M NR	300 mg tid	12m	ADAS-Cog BfS CGI DSST ECG GBS Laboratory tests MMSE NAA NAB SKT Syndrome Short Test Zerssen Adjective Mood Scale	AD vs VaD
Mielke 1996	IS	5	Placebo Propentofylline	DSM-III-R	VaD	Mild-Mod	30	25	68.7y (55-79y) 58%M	300 mg tid	3m	DSST Fragmented Picture Task Memory Tasks MMSE PET Physiological tests	No
Mielke 1998	NR	5	Placebo Propentofylline	NINCDS DSM-III-R	AD	Probable Mild-Mod	30	28	64.8y (52-78y) 57%M	300 mg tid	3m	DSST FAST MMSE PET BSRT SRT-DR Verbal Fluency	No

EvTable201. Key characteristics: Propentofylline cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male Population	Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Saletu 1990 Auxiliary: Moller 1994	NR	6	Placebo HWA 285 (Propentofylline)	DSM-III-R	Dementia	Mild	190	165	68.5y (NR) 49%M	300 mg tid	12w	Alphabetical Cross-out test Benton Test CGI-CGC CGI-S Cognitive Difficulties Scale CT DST EEG Folstein Mini-Mental State GBS Gruenberger Verbal Memory Test MMSE MRI Pictures of Objects Task and Learning Trail Making Test	MMSE

EvTable202. Study results: Propentofylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6m**		**Final: (specify) 12m**	
Marcusson 1997	ITT Analysis 1] Placebo change from baseline 2] Propentofylline 300 mg tid change from baseline 3] Change from baseline in treatment vs placebo	<u>GBS</u>			1] 1.5 (12.5) 2] -2.2 (11.1)	3] 0.003	1] 4.5 (15.5) 2] -0.4 (14.2)	3] 0.001
		<u>CGI item II</u>			1] -0.4 (2.3) 2] -1.0 (2.7)	3] 0.028	1] -0.3 (4.0) 2] -1.2 (5.1)	3] 0.072
		<u>SKT</u>			1] -0.4 (3.9) 2] -1.9 (3.4)	3] 0.001	1] -0.1 (3.8) 2] -1.5 (3.9)	3] 0.002
		CGI item I			1] 0.03 (0.6) 2] -0.14 (0.6)	3] 0.014	1] 0.09 (0.7) 2] -0.12 (0.8)	3] 0.004
		MMSE			1] 0.4 (3.5) 2] 0.9 (3.1)	3] 0.072	1] -0.6 (4.2) 2] 0.6 (3.9)	3] 0.001
		DSST			1] -0.5 (6.0) 2] 0.6 (6.9)	3] 0.222	1] -0.9 (6.5) 2] 1.1 (8.2)	3] 0.062
		NAB			1] 1.1 (3.4) 2] 0.1 (3.4)	3] 0.021	1] 6.8 (3.7) 2] 0.6 (3.8)	3] 0.007
		NAA			1] -0.3 (4.7) 2] -0.0(4.3)	3] 0.395	1] 0.9 (4.9) 2] -0.2 (5.1)	3] 0.698
		BfS			1] 0.1 (10.6) 2] -1.5 (9.4)	3] 0.588	1] -0.1 (10.1) 2] -1.2 (9.9)	3] 0.893

EvTable203. Study results: Propentofylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Mielke, 1996	OC Analysis 1] Placebo change from baseline 2] Propentofylline 300 mg tid change from baseline 3] Propentofylline 300 mg tid vs Placebo	MMSE DSST		3] NS 3] NS			1] 21.9 (3.1) 2] 21.4 (3.2) 1] 19.6 (8.1) 2] 15.6 (7.5)	3] <0.1 3] <0.1

EvTable204. Study results: Propentofylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 3m	
Mielke, 1998	OC Analysis 1] Placebo change from baseline 2] Propentofylline 300 mg tid change from baseline 3] Change from baseline in treatment vs placebo	MMSE	1] 21.3 (3.4) 2] 19.5 (3.5)				1] -1.0 (1.6) 2] -1.4 (3.8)	1] NS 2] 0.02 3] NS
		BSRT					1] 0.1 (0.7) 2] -0.1 (0.5)	1] NS 2] NS 3] NS
		SRT DR					1] 0.4 (1.1) 2] 0.5 (1.3)	1] NS 2] NS 3] NS
		DSST					1] -2.1 (7.5) 2] 3.2 (6.2)	1] NS 2] NS 3] <0.06
		Verbal Fluency					1] 0.6 (7.5) 2] -1.9 (7.3)	1] NS 2] NS 3] NS

EvTable205. Study results: Propentofylline.

Author Year	Analysis Groups	Test Used	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Saletu, 1990	OC Analysis 1] Placebo 2] Propentofylline 300mg tid	GBS Total	1] 26.2 (11.1) 2] 29.4 (14.8)	5] 0.1632			3] -2.5 (10.4) 4] -11.6 (11.8)	3]<0.05 4] <0.05 5] 0.0001
Moller 1994	3] Placebo change from baseline 4] Propentolfylline change from baseline 5] Placebo vs Propentofylline	MMSE	1] 20.9 (2.3) 2] 21.0 (2.7)	5] 0.8794			3] 2.3 (4.0) 4] 4.2 (3.2)	3]<0.05 4]<0.05 5] 0.0038
		CGI –S	1] 5.06 (.71) 2] 5.19 (.74)	5] 0.619			3] -0.50 (1.20) 4] -0.82 (1.00)	3] <0.05 4] <0.05 5] 0.014
		CGI-CGC					3] 4.02 (1.37) 4] 3.33 (0.97)	3] <0.05 4] <0.05 5] 0.003
		CGI-efficacy					3] 2.70 (1.05) 4] 2.31 (1.04)	3] <0.05 4] <0.05 5] 0.032
		8 Psychometric tests				5] NS		3] 0.05 4] 0.05 5] NS

EvTable206. Adverse Events: Propentofylline.

Adverse events (AE) identified in included studies	Marcusson{1984}, 1997	Mielke{2645}, 1996	Mielke{1855}, 1998	Saletu{4169}, 1990
Withdrawn (%) due to AE	T: 12 C: 8	T: 0 C: 0	T: 8 C: 0	T: 0 C: 13
AE Checklist (Max 5)	2	4	2	1
None Reported		X		
Balance				
Accidental Injury				
Dizziness	X			X
Falls				
Behavioral				
Agitation				
Cardiovascular				
Arrhythmia				
Hypotension				
Hypertension				
Extrapyramidal				
Tremor				
Gastrointestinal	X			X
Abdominal pain	X		X	
Constipation				
Diarrhea				
Dyspepsia				
Nausea, vomiting	X			
Metabolic/nutritional				
Eating disorder				
Weight Change				
Neurological				
Asthenia				
Psychiatric				
Anxiety				X
Confusion, delirium				
Depression				
Respiratory				
Cough, cold, infection				
Rhinitis				
Other				
Aberrant hematology				
Fatigue, weakness				
Fever, flu, pneumonia				
Headache	X			X
Hepatic abnormality				
Muscle/joint disorder				
Pain				
Rash, skin disorder			X	
Sleep disorder				
Urinary disorder				

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable207. Key characteristics: Other agents.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Senin 1991	PI	8	Placebo Aniracetam	NINCDS	AD	Mild-Mod	109	109	72.4y (65-80y) 44%M 100% Community	750 mg bid	6m	Blessed-D Corsi Test Gibson Spiral Maze MMSE Raven Colored Progressive Matrices Rey's 15 SCAG TP	No
Ban 1991b	NR	5	Placebo Ateroid	DSM III	PDD MID SDAT	NR	155	148	73.0 y (NR) 56% M 30% Community 70% Institution	200 LRU tid	12w	SCAG HDS Laboratory tests	PDD vs MID
Shrotriya 1996	IF	6	Placebo BMY (Nootropic)	NINCDS DSM-III-R	AD	Mild-Mod	69	54	72.0 y (54-92 y) 41% M	300 mg tid	12w + 4w washout	ADAS ADAS-Cog AE CGI-S CNTB MMSE	No
Cucinotta 1992	NR	6	Placebo Buflomedil	DSM-III-R	VaD	Mild-Mod	88	73	74.0 y (NR) 47% M	300 mg bid	270d	Birren test CGI Dementia rating scale HDS HIS MMSE Nowlis mood test SHGRS	No

EvTable207. Key characteristics: Other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Danielczyk 1988	NR	8	Placebo CBM 36-733 (Ergokryptine)	DSM III	PDD	Mild-Mod	125	117	73.8 y (60-90 y) 41% M Community Institution	0.4 mg/d (Day 1-3) 0.8 mg/d (Day 4-6) 1.2 mg/d (Day 7-9) 2 mg/d (Day 10-end)	8w	Digit span Laboratory tests Neuropsychological Battery NOSIE Psychometric tests SCAG Trail Making Test WAIS	No
Shimada 1994	NI IS	5	Placebo Choto-san	DSM-III-R	VaD	NR	60	57	78.9 y (NR) 15% M 100% Asian 77% Cardiovascular 5% Diabetes 5% Parkinson's 5% Liver/Renal	2.5 g tid	12w	Global improvement rating Hasegawa's dementia scale Overall safety rating Utility rating	No
Terasawa 1997	PI	5	Placebo Choto-san	DSM-III-R	VaD	NR	139	119	76.6 y (NR) 36 100% Asian; 80% Cardiovascular 8% Diabetes 5% Parkinson's 3% Liver/Renal	7.5 g tid	12w	HDS-R Various Global Rating Scales	No
Schellenberg 1997	PI	5	Placebo Cyclandelate	DSM-III-R	AD	NR	139	92	75.0 y (62-85 y) 21% M Community	400 mg qid	16w	ADAS FIGT MEMT NCT NSL NST SCAG	No

EvTable207. Key characteristics: Other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Weyer 2000	PI	7	Placebo Cyclandelate	DSM-III-R	PDD VaD Mixed	Mild-Modly Sev	196	147	78.6 y (54-91y) 27% M Community	800 mg bid	24w	ADAS-Cog CGI-C NOSGER-IADL	MMSE ADAS-Cog Treatment Centre
Peabody 1986	NI IS	6	Placebo Vasopressin (DAVP)	DSM III	PDD	Mild-Mod	14	NR	NR	30 µg/d (start) 180 µg/d	3w	BUSCHKE-S&L SCAG HAM-D POMS VAMS	No
Cucinotta 1996 Auxiliary: Cucinotta 1998	IF	6	Placebo Ergokryptine (DEK)	NINCDS	AD	Mild-Mod	215	155	74.0 y (60-85 y) 33% M Italian, Institution	5 mg bid (week 1-2) 10 mg bid (week 3-4) 20 mg bid (until end)	1y	AE GBS HAM-D MDB MMSE Rey	No
Treves 1999	NR	5	Placebo Denbufylline	DSM-III-R	VaD AD MIXED	Mild-Mod	336	229	74.0 y (>60 y) 42% M	100 mg bid	16w	MMSE WAIS-DSST WAIS-VDC	No
Crapper-McLachlan 1991	NI	7	Placebo DFO	NINCDS	AD	Probable	48	39	63.1y (57-69 y) 49% M 100% Community	500 mg bid (start) 125 mg bid (Day 17-end)	2y	VHB Wechsler Adult Intelligence-revised verbal Wechsler Memory Scale Western Aphasia Battery	No

EvTable207. Key characteristics: Other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Scharf 1999	NI IS	7	Placebo Diclofenac & Misoprostol	DSM IV	AD	Mild-Mod	41	26	73.0 y (≥50 y) 44% M Community	50 mg & 200 µg bid	25w	ADAS-Cog ADAS-Noncog ADAS-total CGIC GCIC GDS IADL MMSE PSMS	No
Ban 1991a	IS	7	Placebo Glycosamino-glycan Polysulphate	DSM III	PDD MID	Mod-Sev	155	148	73.5 y (56-98 y) 57% M Hispanic, Italian 30% Community 70% Institution	200 LRU tid	12w	ADL BPRS CGI-GI CGI-SI CT EEG EKG GDS HDS HIS MMSE SCAG WMS-RR	No

EvTable207. Key characteristics: Other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population (	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Ala 1990	PI	5	Placebo GM-1 Monosialotetrahexosylgan	NINCDS	AD	Mild-Mod	46	42	71.0 y (63-79 y) 39% M	100 mg/d	12w	BCRS Benton Racial Recognition Test BPRS Buschke Selective Reminding Test Clock drawing Complex Figure Test Grooved pegboard test HAM-D IADL Letter cancellation Lipids MMSE NOSIE Selective Reminding Symbol-Digit Modalities test Verbal fluency	No
Crook 1992b	NR	5	Placebo Guanfacine	NINCDS DSM III	AD PDD	Mild-Mod	29	26	71.0 y (60-81y) 45% M Community	0.5 mg/d	13w	Benton Visual Retention CGI variables MMSE Neuropsychiatric rating scale WAIS Vocabulary Wechsler Paired Assoc.	No
Thompson 1990	IF	7	Placebo Hydergine-LC	DSM III NINCDS	PDD AD	Probable	80	68	71.0 y (55-79 y) 59% M	1 mg tid	24w + 2w wash out	GERRI Ham-D IPSCE SCAG WMS WAIS-DSST	No

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total # Randomized	# Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Van Gool 2001	NI IS	8	Placebo Hydroxychloro-quine	NINCDS	AD	Min-Mild	168	155	70.6 y (NR) 42% M	400 mg/d if >/= 65 kg 200 mg/d if </= 65 kg	18m	ADAS-Cog CAMDEX IDDD RMBPC	No
Rogers 1993	NR	5	Placebo Indomethacin	NINCDS	AD	Mild-Mod	44	28	78.0 y (NR) 54% M Community	100 mg/d if </= 100 lbs 125/d if 101150 lbs 150 mg/d if >/= 150 lbs	6m	ADAS BNT MMSE TK	No
Adair 2001	NI	7	Placebo N-acetylcysteine	NINCDS	AD	Mild-Mod	47	43	NR Community	50 mg/kg/d	6m	ADL BNT CT Scan MMSE Neuropsychological Battery	No
Aisen 2002	NI	7	Placebo Nimesulide	DSM III	AD	Probable	40	38	74.0 y (NR) 58% M	100 mg bid	12w	ADAS-Cog ADL BPRS CDR HAM-D MMSE	No

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Ban 1990	IS	7	Placebo Nimodipine	DSM III	PDD MID	Mild- Modly Sev	178	175	75.4 y (55-95 y) 42% M Italian, 19% Community 79% Institution	90 mg/d	12w	CBC & platelet count CGI Severity of illness CGI-global improvement EEG GDS HAM-D HIS Laboratory tests MMSE Neurologic Evaluation Plutchik Geriatric Rating Scale SCAG Wechsler Memory Scale	No
Pantoni 2000a Auxiliary: Pantoni 2000	IF	6	Placebo Nimodipine	DSM-III-R	MID	Mild-Mod	259	251	74.3 y (45-85 y) 47% M White, Community & Institution	30 mg tid	26w	ADL CDR CGI Digit Span Fuld Object Memory GBS IADL MMSE RDS Word Fluency ZVT-G	VaD vs MID

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Carlson 2001 Auxiliary: Breitner 1999	IS	7	Placebo Nizatidine	DSM-III-R NINCDS NINDS-AIREN	AD VaD	Probable – Possible	51	42	80.7 y (67-96 y) 38% M	75 mg bid	1y	Benton Visual Retention Test Boston Naming Test Category Fluency CERAD Constructional Praxis COWA CPT IADL Logical Memory I & 2 MMSE MMSE Trail-Making Test WLM WMS WMS-R	No
Kragh-Sorensen 1986	NI	6	Placebo ORG 2766	DSM III	PDSD	Mild-Mod	156	126	82.5 y (>65 y) 23% M	80 mg bid	28d	GAGS Laboratory tests LPRS RDS SCAG	No

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Soininen 1985 Auxiliary Partanen 1986 Soininen 1984	IS	7	Placebo ORG 2766	DSM III	AD	Mild-Sev	77	73	73.2 y (NR) 32% M Institution	20 mg bid	6m	AGS-E GPI-E LPRS McGBRS SCAG	No
Aisen 2000b Auxiliary: Aisen 2000a	NI IS	7	Placebo Prednisone	NINCDS	AD	Mild-Mod	138	92	72.3 y (>50 y) 69% M	20 mg/d (week 1-4) 10 mg/d (week 5-end)	1y	ADAS-Cog BDRS BPRS CDR-SB HAM-D MMSE	No
Simmons 2002	PI IS	7	Placebo Simvastatin	NINCDS	AD	Mild-Mod	44	37	68.3 y (60-77 y) 43% M	80 mg/d	26w	ADAS-cog Laboratory tests MMSE	MMSE

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Nolan 1991	NI	5	Placebo Thiamine	NINCDS	AD	Mild-Mod	15	10	76.3 y (59-87 y) 33% M Community	3 g/day	12m	Boston Naming test CERAD Constructional praxis test Delayed recall and recognition MMSE Verbal learning score Word list learning test	No
Fischhof 1996	NR	5	Placebo Vincamine	DSM-III-R	PDD VaD	Mild-Mod	152	142	Mean NR (50-85 y) % M NR Institution	30 mg bid	12w	BGP CGI SCAG SKT	MID vs DAT
Croisile 1993	IF	4	Placebo Piracetam	NINCDS	AD	Mild-Mod	33	30	42% M Community	8 gr/day per oz	1y	Aphasia Battery Blessed A CT EEG Laboratory tests Logical Digit Span MADRS MMSE Neuropsychological Battery	No

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Kanowski 1990	PI	8	Placebo Xantinol nicotinate	DSM-III-R	AD MID	Mild-Mod	313	297	82.0 y (≥60 y) 19% M	1g tid	12w	BGP CGI NAI SCAG Digit Correction Test Digit Symbol Substitution Test	MID vs DAT
Thomas 2001	NR	7	Donepezil Vitamin E Rivastigmine (open label)	NINCDS	AD	Mild-Mod	60	54	66.1y (57-78 y) 44% M	Donepezil: 5 mg/d (1 month) 10 mg/d (until end) Vitamin E: 2000 IU (fixed)	6m	ADAS-cog CT/MRI ERP scalp topography GBS GDS MMSE NPI WAIS	No
Taragano 1997	NR	7	Fluoxetine Amitriptyline	NINCDS DSM III	AD	Mild-Mod	37	25	72.0 y (NR) 22% M Community, Major depression	10 mg/d 25 mg/d	45d	HAM-D MMSE	No
Passeri 1993	NR	5	5'-MTHF (folate) Tradozone	DSM III-R	AD MID	Mild-Mod	96	96	Mean NR (65-94 y) 45% M Depression	50 mg/d 100 mg/d	8w	Blood levels HDRS RVM – immediate recall RVM – delayed recall	AD vs MID

EvTable207. Key characteristics: Various other agents cont'd.

Author Year	Funding Source	Quality Score	Interventions	Criteria for Diagnosis	Diagnosis	Disease Severity	Total Number Randomized	Number Completing Trial	Mean age (range) % Male (M) Population	Highest Dose	Treatment Period	Outcomes Measured	Outcome reports stratified
Parnetti 1995	NR	6	Placebo Posatirelin Citicoline	NINCDS	AD	Mild-Mod	222	214	74.9 y (65-85 y) 34% M 100% Community	10 mg/d 500 mg/d	3m	GBS GDS HDRS MMSE Laboratory tests	No
Spilich 1996	PI	6	Pyritinol Hydergine	NINCDS	AD	Mild-Mod	102	100	73.0 y (NR) 31% M 100% Hispanic	600 mg/d 4.5 mg/d	12w	CETM SCAG	No
Cucinotta 1988	PI	5	Sulfomuco-polysaccharides CDP-choline	DSM III	MID	Mild-Mod	30	23	79.4 y (NR) 27% M 100% Institution	500 LRU 1000 mg	4w	Blessed-D Digit-Span Digit-Symbol NMS SCAG TP	No
Parnetti 1997	NR	5	Sulodexide Pentoxifylline	NINDS-AIREN	VaD	Mild-Mod	93	86	75.0 y (65-80 y) 40% M Institution	100 mg/d 1200 mg/d	6m	GBS Laboratory tests MMSE	No
Sano 1997 Auxiliary: Thal 1996	NI IS	5	Placebo Vitamin E Selegiline Selegiline + VitaminE	NINCDS	AD	Mod	341	341	73.4 y (NR) 35% M	Vitamin E 1000 IU bid Selegiline 5mg bid	2y	ADAS-Cog Blessed Dementia Scale CDR MMSE Time to end-point (event free survival)	No

EvTable208. Study results: Aniracetam

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 4m		Final: (specify) 6m	
Senin 1991	OC Analysis 1] Placebo 2] Aniracetam 1500 mg/d 3] Placebo time x baseline 4] Aniracetam time x baseline 5] Placebo vs. Aniracetam	SCAG total	1] 48.2 (1.3)* 2] 50.5 (0.9)*		1] 52.2 (1.6)* 2] 42.3 (1.5)*	3] <0.01 4] <0.001 5] <0.001	1] 56.5 (2.3) 2] 39.4 (1.5)	3] <0.01 4] <0.001 5] <0.001
		Blessed I	1] 7.2 (0.4)* 2] 7.9 (0.4)*		1] 7.9 (0.4)* 2] 6.3 (0.5)*	3] <0.001 4] <0.001 5] <0.02	1] 8.8 (0.5) 2] 5.7 (0.5)	3] <0.001 4] <0.001 5] <0.001
		Blessed II	1] 22.9 (0.5)* 2] 21.6 (0.6)*		1] 21.5 (0.8)* 2] 24.4 (0.8)*	3] <0.001 4] <0.001 5] <0.01	1] 20.2 (1) 2] 26.1 (0.6)	3] <0.001 4] <0.001 5] <0.001
		Toulouse-Pieron (global)	1] 0.4 (0.1)* 2] 0.3 (0.08)*		1] 0.1 (0.1)* 2] 0.7 (0.08)*	3] <0.02 4] <0.02 5] <0.001	1] 0.2 (.01) 2] 0.8 (.01)	3] <0.02 4] <0.001 5] <0.001
		Rey immediate recall	1] 18.4 (0.9)* 2] 16.9 (0.9)*		] 16.2 (0.9)* 2] 20.8 (1)*	5] <0.001	1] 16.2 (1.1) 2] 23.4 (1)	3] 0.001 4] <0.001 5] <0.001
		Rey delayed recall	1] 1.9 (0.2)* 2] 1.8 (0.2)*		1] 1.3 (0.2)* 2] 2.6 (0.3)*	5] <0.02	1] 1.6 (0.3) 2] 2.9 (0.4)	3] <0.001 4] <0.001 5] <0.02

*SEM

EvTable209. Study results: Ateroid.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Ban 1991b	OC Analysis 1] Placebo 2] Ateriod 200LRU tid 3] Ateriod vs Placebo	SCAG total SCAG cognitive SCAG agitation SCAG overall impression SCAG depression HDS					1] 17.3 2] 24.1 1] 13.0 2] 19.2 1] 17.77 2] 25.4 1] 13.5 2] 20.2 1] 22.0 2] 27.5	3] <0.05 3] <0.05 3] NS 3] <0.10 3] <0.10 3] <0.04

EvTable210. Study results: BMY 21,502.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
Shrotrya, 1996	OC Analysis 1] Placebo 2] BMY 21,502 300 mg tid 3] BMY 21,502 300 mg tid vs Placebo 4] Placebo changes from baseline 5] BMY changes from baseline	<u>ADAS-Cog</u> <u>CGI severity</u> MMSE CGI % Improvement	1] 16.2 2] 15.1 1] 3.49 2] 3.29 1] 22.5 2] 23.5	3] 0.81 3] 0.11 3] 0.26			4] -0.5 5] -1.5 1] 28% 2] 37%	3] >0.05 3] NS 3] >0.05

EvTable211. Study results: Buflomedil.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 90d**		**Final: (specify) 270d**	
Cucinotta, 1992	OC Analysis 1] Group I Buflomedil 300mg/ bid 270d 2] Group II Buflomedil 300mg/ bid 180d No treatment 90d 3] Group III Placebo 90d Buflomedil 300mg bid 180d 4] Group IV Placebo 90d Buflomedil 300mg/ bid 90d No treatment 90d	SHGRS Median Rating scale & Neuro- psychological test scores Dementia Rating scale Birren test Nowlis Mood test Clinical Global Impression	1] 43.00 2] 35.50 3] 29.00 4] 41.00 1] 16.00 2] 18.50 3] 21.50 4] 29.00 1] 39.00 2] 22.50 3] 27.00 4] 37.25 1] 1.19 2] 1.38 3] 1.83 4] 1.27 1] 13.38 2] 13.17 3] 15.83 4] 15.50 1] 025 2] 0.00 3] 0.00 4] 0.03		1] 37.00 2] 30.50 3] 25.40 4] 39.00 1] 10.75 2] 16.50 3] 9.50 4] 22.50 1] 28.00 2] 18.50 3] 22.00 4] 30.25 1] 1.64 2] 2.50 3] 1.93 4] 1.50 1] 12.12 2] 12.00 3] 12.50 4] 15.75 1] 0.82 2] 1.00 3] 0.12 4] 0.05		1] 29.00 2] 30.00 3] 23.75 4] 34.00 1] 6.25 2] 11.50 3] 7.00 4] 22.00 1] 15.25 2] 17.50 3] 15.75 4] 28.00 1]1.33 2] 0.67 3] 0.67 4] 0.00	

EvTable212. Study results: CBM 36-733 (Ergokryptine).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 8w	
Danielczyk, 1997	OC Analysis 1] Placebo 2] CBM 36-733 2.0 mg/d 3] Differences between groups	 SCAG-Overall Impression SCAG-Cognitive Dysfunction SCAG-Interpersonal Relationship SCAG-Apathy SCAG-Affect SCAG-Somatic Dysfunction Psychometric Test Battery -tests with significant difference	 1] 5.0 2] 5.0 1] 18.0 2] 16.0 1] 12.0 2] 10.0 1] 14.0 2] 15.0 1] 10.0 2] 9.0 1] 8.0 2] 7.0				 1] 5.0 2] 4.0 1] 17.0 2] 15.0 1] 11.0 2] 8.0 1] 14.0 2] 13.0 1] 10.0 2] 8.0 1] 7.0 2] 7.0 2/9	 3] 0.016 3] 0.276 3] 0.421 3] 0.011 3] 0.385 3] 0.679

EvTable213. Study results: Choto-san.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 8w		Final: (specify) 12w	
Shimada 1994	OC Analysis 1] Placebo 2] Choto-san 2.5g tid 3] Difference between Placebo and Choto-san 4] Choto-san vs baseline	Global Improvement rating (% improved) Utility rating (% useful) Global improvement -subjective symptoms -neurological symptoms -psychiatric symptoms Disturbance in daily living Hasegawa dementia	 1] 15 (3.84) 2] 15 (3.76	 4] NS	 1] 19% 2] 61% 1] 12% 2] 59% 1] 13% 2] 5% 1] 12% 2] 58% 1] 12% 2] 29% 1] 16 (5.82) 2] 18 (4.79)	 3] <0.01 3] <0.01 3] NS 3] <0.01 4] <0.01	 1] 23% 2] 71% 1] 25% 2] 78% 1] 21% 2] 55% 1] 25% 2] 14% 1] 24% 2] 58% 1] 19% 2] 38% 1] 17 (5.97) 2] 19 (5.71)	 3] <0.01 3] <0.01 3] <0.01 3] NS 3] <0.01 3] <0.05 4] <0.01

EvTable214. Study results: Choto-san.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 8w**		**Final: (specify) 12w**	
Terasawa 1997	OC Analysis 1] Placebo 2] Choto-san 2.5g tid 3] difference between Placebo and Choto-san	Global severity rating %improved HDS-R Utility Rating (% Useful)			1] 42.9% 2] 70.9% 1] 17.3(5.3) 2] 18.0(6.4)	3] 0.001 3] NS	1] 48.4% 2] 34.4% 1] 17.4(6.0) 2] 19.3(6.6) 1] 33% 2] 44%	3] <0.001 3] NS 3] <0.001

EvTable215. Study results: Cyclandelate.

Author Year	Analysis Groups	Ooutcomes Meassured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 8w		Final: (specify) 16w	
Schellenberg 1997	ITT Analysis 1] Placebo 2] Cyclandelate 1,600 mg d 3] Cyclandelate vs. placebo	SCAG	1] 44.0 (39.0, 53.0) 2] 39.0 (35.0, 51.0)		1] 36.0 (28.0, 53.0) 2] 33.0 (28.0, 38.0)		1] 38.0 (29.0, 67.0) 2] 32.0 (26.0, 37.0)	3] 0.0004
		ADAS	1] 24.0 (15.0, 39.0) 2] 20.0 (14.0, 37.0)		1] 20.0 (13.0, 34.0) 2] 17.0 (9.0, 22.0)		1] 17.0 (11.0, 42.0) 2] 16.0 (8.0, 20.0)	3] 0.0006
		NCT	1] 16.5 (8.0, 35.0) 2] 20.2 (10.2, 32.2)		1] 25.8 (10.8, 51.2) 2] 37.2 (22.6, 54.0)		1] 34.9 (11.4, 52.8) 2] 26.4 (19.4, 53.4)	3] >0.2
		NST	1] 39.0 (19.0, 59.0) 2] 48.0 (27.0, 57.0)		1] 50.0 (23.0, 65.0) 2] 56.0 (39.0, 68.0)		1] 54.0 (27.0, 65.0) 2] 59.5 (36.0, 66.0)	3] 0.0051
		FIGT	1] 14.5 (7.0, 34.0) 2] 22.0 (13.0, 34.0)		1] 25.5 (11.0, 45.0) 2] 33.5 (18.0, 49.0)		1] 30.0 (11.0, 45.0) 2] 31.5 (18.0, 45.0)	3] >0.2
		MEMT	1] 17.0 (12.0, 19.0) 2] 18.0 (14.0, 19.0)		1] 18.0 (14.0, 19.0) 2] 18.0 (17.0, 19.0)		1] 18.0 (15.0, 19.0) 2] 18.0 (16.0, 19.0)	3] >0.2
		NSL	1] 53.0 (45.0, 61.0) 2] 49.0 (43.0, 58.0)		1] 51.0 (38.0, 63.0) 2] 41.0 36.0, 50.0)		1] 55.0 39.0, 69.0) 2] 41.0 (27.0, 49.0)	3] .000002

EvTable216. Study results: Cyclandelate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 24w**	
Weyer, 2000	ITT Analysis 1] Placebo change from baseline 2] Cyclandelate 800 mg bid change from baseline 3] Difference between Placebo and Cyclandelate in change from baseline	ADAS-Cog% responders < -10 points NOSGER-IADL % responders < -5 points CGI-C % responders at least minimal improvement ADAS-Cog NOSGER-IADL					1] 12.8% 2] 18.6% 1] 5.3% 2] 10.3% 1] 51.1% 2] 58.8% 1] -1.5 (7.4) 2] -2.7 (8.8) 1] -0.2 (2.7) 2] -0.6 (3.9)	3] NS 3] NS 3] NS 3] 0.320 3] 0.181

EvTable217. Study results: Desamino-D-Arginine-Vasapressin (DDAVP).

Author Year	Analysis Groups	Outcomes Measusred	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 3w	
Peabody 1986	OC Analysis 1] Placebo 2] DDAVP 45mg qid 3] DDAVP vs Placebo	HAM-D	1] 4.4 (4.6) 2] 3.2 (3.6)				1] 3.6 (2.8) 2] 4.5 (3.9)	3] 0.02
		SCAG affect	1] 4.1 (1.3) 2] 4.6 (1.8)				1] 4.4 (1.2) 2] 4.7 (2.6)	3] 0.01
		SCAG interpersonal	1] 4.8 (1.2) 2] 4.6 (1.0)				1] 4.5 (0.4) 2] 5.0 (1.5)	3] 0.02
		SCAG 19 (overall)	1] 4.4 (0.7) 2] 3.4 (1.0)				1] 4.5 (0.6) 2] 3.3 (1.1)	3] 0.06
		SCAG total	1] 36 (5) 2] 29 (6)				1] 35 (3) 2] 30 (65)	3] NS
		Buschke total recall	1] 6.1 (1.8) 2] 7.4 (2.1)				1] 5.8 (2.0) 2] 7.7 (2.5)	3] NS
		POMS Vigor	1] 55 (9) 2] 59 (7)				1] 56 (9) 2] 63 (6)	3] NS
		POMS Fatigue	1] 42 (5) 2] 42 (5)				1] 44 (6) 2] 41 (5)	3] NS
		POMS Depression	1] 37 (4) 2] 38 (5)				1] 37 (3) 2] 38 (5)	3] NS

EvTable218. Study results: Dihydroergokryptine (DEK).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 6m		Final: (specify) 12m	
Cucinotta, 1996 Cucinotta, 1998	Endpoint Analysis 1] Placebo 2] DEK 20mg bid 3] DEK 20mg bid vs Placebo	<u>GBS Factor 1</u>	1] 8.7 (4.4) 2] 9.6 (4.3)		1] 9.4 (4.4) 2] 8.4 (4.2)		1] 10.5 (4.8) 2] 8.0 (4.8)	3] 0.000
		<u>GBS Factor 2</u>	1] 5.2 (6.0) 2] 4.9 (5.7)		1] 5.4 (6.2) 2] 4.1 (4.6)		1] 7.2 (7.7) 2] 3.8 (4.7)	3] 0.001
		<u>GBS Factor 3</u>	1] 3.5 (2.7) 2] 3.3 (2.4)		1] 3.1 (2.3) 2] 2.7 (2.3)		1] 3.0 (2.8) 2] 2.5 (2.3)	3] 0.229
		<u>GBS Factor 4</u>	1] 13.1 (7.5) 2] 12.6 (7.6)		1] 13.5 (7.8) 2] 11.1 (6.7)		1] 15.3 (7.5) 2] 10.3 (6.7)	3] 0.000
		MMSE	1] 19.6 (2.6) 2] 19.7 (2.6)	3] 0.645			1] 8% reduction 2] same mean	3] <0.001
		HAM-D	1] 9.1 (4.9) 2] 9.4 (4.7)	3] 0.621				
		REY Test Immediate Recall	1] 14.4 (7.0) 2] 14.3 (7.9)		1] 12.2 (7.2) 2] 14.2 (8.3)		1] 11.7 (7.0) 2] 14.5 (8.1)	3] 0.022
		REY Test Delayed Recall	1] 3.0 (2.9) 2] 3.4 (2.5)		1] 3.0 (3.0) 2] 3.8 (3.4)		1] 2.4 (2.7) 2] 4.0 (3.7)	3] 0.044
		GBS-C	1] 4.7 (2.8) 2] 4.9 (5.7)		1] 4.9 (3.3) 2] 4.1 (2.6)		1] 5.4 (3.3) 2] 3.6 (2.6)	3] 0.004
		GBS – M	1] 5.2 (6.0) 2] 4.9 (5.7)		1] 5.4 (6.2) 2] 4.1 (4.6)		1] 7.2 (7.7) 2] 3.8 (4.7)	3] 0.001
		GBS - I	1] 18.8 (8.9) 2] 19.1 (9.2)		1] 19.8 (8.8) 2] 16.8 (8.2)		1] 22.3 (8.9) 2] 16.6 (9.0)	3] 0.000

EvTable219. Study results: Denbufylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 16w**	
Treves, 1999	OC Analysis 1] Placebo 2] Denbufylline 25 mg bid 3] Denbufylline 50 mg bid 4] Denbufylline 100 mg bid 5] Denbufylline Overall doses 6] Treatment effect vs Placebo	<u>MMSE</u> <u>DSST</u> WAIS-voc	1] 17.3 (4.2) 2] 18.4 (4.6) 3] 18.6 (4.7) 4] 18.2 (4.8) 5] 18.4 (4.7) 1] 6.6 (6.8) 2] 7.2 (6.5) 3] 8.5 (8.6) 4] 7.5 (5.4) 5] 7.7 (6.9) 1] 28.9 (15.5) 2] 28.8 (17.2) 3] 26.6 (17.1) 4] 27.7 (16.1) 5] 27.7 (16.8)				1] 16.9 (5.1) 2] 19.5 (6) 3] 19.1 (5.7) 4] 19.1 (5.5) 5] 19.3 (5.7) 1] 7.1 (7.1) 2] 9.4 (9) 3] 9.7 (8.6) 4] 8.3 (7.6) 5] 9.2 (8.5) 1] 26.1 (16) 2] 30.9 (19.6) 3] 29.4 (19.3) 4] 29.6 (19.4) 5] 30.0 (19.4)	6] 0.7 6] NS 6] NS

EvTable220. Study results: Desferrioxamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 18m	
Crapper McLachlan 1991	OC Analysis 1] Placebo slope of change from baseline 2] Desferrioxamine 500 mg BID slope of change from baseline 3] Difference from baseline between Desferrioxamine and Placebo	VHB	1] -1.717 (1.689)				1] -0.866 (0.932)	3] 0.0375

EvTable221. Study results: Diclofenac and Misoprostol (D/M).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 25w**	
Scharf 1999	ITT Analysis 1] Placebo 2] Diclofenac 50mg and Misoprostol 200µg (D/M) 3] Placebo mean change from baseline 4] D/M group mean change from baseline 5] mean treatment differences placebo vs. D/M	ADAS-cog GDS CGIC MMSE ADAS-noncog ADAS-Total IADL PSMS CGIC-C Caregiver rated					3] 1.93 (5.55) 4] 0.25 (4.50) 3] 0.57 (0.51) 4] 0.35 (0.49) 3] 4.57 (0.51) 4] 4.29 (0.69) 3] -0.86 (3.21) 4] 0.41 (2.69) 3] 1.36 (3.93) 4] -0.59 (3.89) 3] 3.24 (8.85) 4] -0.75 (1.34) 3] 1.86 (2.03) 4] 0.06 (2.95) 3] 0.21 (0.89) 4] 0.53 (1.84) 3] 4.79 (1.05) 4] 4.47 (1.01)	5] 0.571 5] 0.384 5] 0.340 5] 0.237 5] 0.319 5] 0.125 5] 0.161 5] 0.340 5] 0.768

EvTable222. Study results: Glycoaminoglycan.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12w**	
Ban, 1991a	OC Analysis 1] Placebo 2] Glycoaminoglycan polysulphate 200 LRU tid 3] Improvement in scores Glycoaminoglycan polysulphate 200 LRU tid vs. placebo	CGI- SI	1] 4.6 (0.69) 2] 4.6 (0.63)				1] 4.0 (0.89) 2] 3.7 (0.77)	3] <0.18
		CGI –GI	1] 3.8 (0.41) 2] 3.7 (0.71)				1] 3.5 (0.71) 2] 3.0 (0.78)	3] <0.001
		BPRS Total scores	1] 31.4 (11.75) 2] 28.9 (12.12)				1] 25.2 (10.73) 2] 20.6 (10.52)	3] <0.01
		ADL	1] 32.9 (9.10) 2] 33.0 (9.77)				1] 32.2 (9.11) 2] 30.5 (9.57)	3] <0.16
		SCAG	1] 56.6 (10.66) 2] 56.1 (13.47)				1] 46.8 (11.78) 2] 42.6 (12.72)	3] <0.05
		MMSE	1] 14.3 (4.64) 2] 14.9 (4.93)				1] 16.2 (5.16) 2] 18.2 (6.01)	3] <0.04
		GDS	1] 4.8 (0.77) 2] 4.8 (0.72)				1] 4.4 (0.95) 2] 4.3 (0.93)	3] <0.50
		HDS	1] 11.8 (3.87) 2] 12.1 (3.98)				1] 11.1(4.28) 2] 10.6 (4.53)	3] <0.04
		WMS-RR PAL	1] 5.9 (3.98) 2] 6.8 (4.7)				1] 5.9 (4.79) 2] 7.7 (4.93)	3] <0.081
		Logical Memory	1] 1.4 (1.42) 2] 1.8 (1.54)				1] 1.5 (1.46) 2] 2.1 (2.01)	3] <0.18
		Immediate Recall	1] 1.5 (1.38) 2] 1.6 (1.55)				1] 1.3 (1.24) 2] 2.0 (2.01)	3] <0.03
		Delayed Recall	1] 0.5 (.22) 2] 0.8 (.23)				1] 0.8 (.36) 2] 1.1 (.31)	3] NS

EvTable223. Study results: **Monosialotetrahexosylgan (GM-1)**.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 12w**		**Final: (specify) 24w**	
Ala 1990	OC Analysis 1] Placebo 2] GM-1 100mg IM d 3] Placebo vs. GM-1 4] Placebo change from baseline 5] GM-1 change from baseline	HAM-D	1] 7.04 (4.01) 2] 5.58 (4.07)		1] 6.61 (4.19) 2] 5.79 (4.61)		1] 6.43 (2.90) 2] 7.21 (4.20)	3] NS 4] >0.05 5]>0.05
		PSM	1] 8.13 (1.63) 2] 8.32 (1.42)		1] 8.09 (1.76) 2] 8.16 (1.80)		1] 9.22 (2.39) 2] 9.42 (2.67)	3] NS 4] 0.032 5] 0.049
		IADL	1] 17.1 (3.2) 2] 18.5 (3.7)		1] 17.4 (3.5) 2] 19.5 (4.1)		1] 18.4 (3.6) 2] 20.6 (4.7)	3] NS 4] 0.012 5] 0.027
		BPRS Total score	1] 8.65 (5.47) 2] 6.42 (3.81)		1] 8.65 (6.32) 2] 8.74 (7.49)		1] 9.22 (4.00) 2] 9.79 (6.33)	3] NS 4] >0.05 5] 0.024
		NOSIE Total score	1] 178 (26) 2] 184 (15)		1] 177 (28) 2] 184 (21)		1] 169 (32) 2] 173 (28)	3] NS 4] 0.031 5] 0.036
		MMSE	1] 17.5 (3.2) 2] 17.5 (3.3)		1] 17.7 (4.4) 2] 18.3 (4.0)		1] 17.0 (4.9) 2] 16.5 (4.5)	3] NS
		BCRS	1] 19.7 (3.3) 2] 19.7 (2.4)		1] 18.9 (2.7) 2] 19.2 (2.6)		1] 19.6 (3.2) 2] 20.3 (2.9)	3] NS
		Complex figure – copy accuracy	1] 10.8 (7.2) 2]11.6 (7.4)		1] 10.7 (6.9) 2] 10.6 (6.5)		1] 9.8 (6.2) 2] 10.7 (7.3)	3] NS

EvTable223. Study results: Monosialotetrahexosylgan (GM-1) cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		**Mid-Point: (specify) 12w**		**Final: (specify) 24w**	
			Verbal fluency	1] 25.1 (9.6) 2] 25.6 (11.1)		1] 26.0 (10.3) 2] 24.4 (11.2)		1] 23.6 (9.4) 2] 22.4 (10.0)	3] NS
			Selective reminding-Retrieval	1] 7.30 (6.96) 2] 9.58 (8.31)		1] 6.35 (6.11) 2] 8.42 (5.69)		1] 9.52 (9.40) 2] 8.95 (6.79)	3] NS
			Symbol digit	1] 11.9 (11.1) 2] 14.6 (8.3)		1] 13.9 (10.8) 2] 15.8 (6.3)		1] 13.8 (10.5) 2] 10.6 (7.4)	3] NS 5] 0.017
			8 other cognitive tests						3] NS

EvTable224. Study results: Guanfacine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 13w	
Crook, 1992b	ITT Analysis 1] Placebo 2] Guanfacine .5mg/d 3] Placebo change from baseline 4] Guanfacine .5mg/d change from baseline 5] Guanfacine .5mg/d change from baseline relative to placebo	CGI Wechsler Paired Associates Benton Visual Retention-Number Correct Benton Visual Retention-Errors	 1] 6.54 (2.04) 2] 6.90 (2.94) 1] 2.69 (1.49) 2] 3.20 (1.66) 1] 15.31 (4.48) 2] 12.73 (6.22)				 3] 6.08 (1.77) 4] 4.97 (2.72) 3] 2.15 (1.57) 4] 1.67 (1.18) 3] 15.69 (5.06) 4] 17.80 (4.28)	 5] <.03

EvTable225. Study results: Hydergine-LC.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 24w	
Thompson 1990	OC Population 1] Placebo change from baseline 2] Hydergine-LC 1mg tid change from baseline 3] Placebo vs Hydergine-LC change from baseline	WAIS DSST WMS-Logical WMS-Visual GERRI IPSCE HAM-D SCAG					1] 1.76(1.64)* 2] 8.85(2.07)* 1] –0.02(0.23)* 2] –0.21(0.23)* 1] –0.07(0.12)* 2] –0.10(0.10)* 1] 0.04(0.07)* 2] –0.23(0.09)* 1] –0.11(1.36)* 2] –1.43(1.65)* 1] 0.46(0.45)* 2] 0.39(0.39)* 1] –3.60(1.35)* 2] –2.37(1.69)*	3] <0.01 3] >0.30 3] >0.50 3] <0.02 3] >0.50 3] >0.50 3] >0.50

*SEM

EvTable226. Study results: Hydroxychloroquine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 9m**		**Final: (specify) 18m**	
Van Gool, 2001	ITT Analysis 1] Placebo	<u>IDDD</u>	1] 10.9 (7.0) 2] 11.6 (7.1)	3] NS	1] 15.9 (9.2) 2] 17.0 (10.0)	3] NS	1] 21.3 (10.5) 2] 22.6 (11.4)	3] NS
	2] Hydroxchloroquine 200 or 400 mg QID	ADAS-Cog	1] 17.6 (9.1) 2] 18.0 (9.4)	3] NS	1] 20.0 (9.70) 2] 21.7 (12.8)	3] NS	1] 25.7 (14.3) 2] 26.4 (14.9)	3] NS
	3] Difference between Placebo and Hydroxchloroquine	RMBPC	1] 27.8 (10.8) 2] 28.6 (11.0)	3] NS	1] 30.2 (11.7) 2] 32.0 (11.5)	3] NS	1] 34.2 (12.4) 2] 36.3 (12.0)	3] NS

EvTable227. Study results: Indomethacin.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6m	
Rogers 1993	Completer Analysis 1] Placebo % change from baseline 2] Indomethacin 150mg/d % change from baseline 3] Difference between Placebo and Indomethacin change from baseline	ADAS MMSE BNT TK Overall all tests					1] –13.3 (5.6)* 2] 1.4 (4.9)* 1] -13.4 (4.4)* 2] -0.9 (4.8)* 1] -6.6 (5.5)* 2] 4.4 (3.7)* 1] -0.4 (2.9)* 2] 0.5 (1.0)* 1] –8.4 (2.3)* 2] 1.3 (1.8)*	3] 0.061 3] 0.069 3] 0.120 3] 0.773 3] <0.003

*SEM

EvTable228. Study results: N-acetylcysteine (NAC).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3m**		**Final: (specify) 6m**	
Adair 2001	ITT Analysis 1] Placebo 2] NAC 50 mg/kg/d 3] Difference between Placebo and NAC	<u>MMSE</u>	1] 18.0 (3.6) 2] 19.8 (3.7)		1] 17.5 (3.6) 2] 20.5 (4.7)	3] 0.056	1] 16.8 (4.6) 2] 19.8 (5.3)	3] NS
		<u>ADL</u>	1] 16.2 (5.0) 2] 14.2 (4.3)		1] 18.5 (4.3) 2] 15.2 (4.7)		1] 20.1 (4.9) 2] 16.1 (5.0)	3] NS
		BNT	1] 18.9 (6.5) 2] 20.9 (5.6)		1] 19.6 (6.0) 2] 21.1 (5.3)		1] 18.0 (6.9) 2] 21.2 (6.2)	3] NS

EvTable229. Study results: Nimesulide.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Aisen 2001	ITT Analysis 1] Placebo 2] Nimesulide 100mg bid 3] Placebo change from baseline 4] Nimesulide change from baseline 5] Nimesulide change from baseline relative to placebo 6] Placebo vs Nimesulide	MMSE ADAS-Cog CDR -SB ADL HAM-D BPRS	1] 22.7 (1.0)* 2] 21.8 (1.1) 1] 21.4 (2.6)* 2] 19.8 (1.5)* 1] 4.6 (0.5)* 2] 4.7 (0.7)* 1] 3.8 (0.5)* 2] 3.3 (.03)* 1] 3.8 (0.8)* 2] 4.6 (0.8)* 1] 29.6 (1.4)* 2] 28.5 (1.5)*	6] 0.54 6] 0.59 6] 0.91 6] 0.34 6] 0.52 6] 0.59			3] -0.5 (1.0)* 4] 0.9 (1.0)* 3] 0.2 (0.3)* 4] 0.7(0.3)* 3] -0.3 (0.2)* 4] -0.2 (0.3)* 3] 1.0 (0.6)* 4] -0.2 (0.9)* 3] 0.4 (0.9)* 4] 0.4 (1.4)*	5] 0.49 5] 0.70 5] 0.73 5] 0.30 5] 0.99

*SEM

EvTable230. Study results: Nimodipine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 90d	
Ban, 1990	OC Analysis 1] Placebo 2] Nimodipine 30 mg bid 3] Nimodipine 30 mg bid vs. placebo	CGI-SI CGI-GI HAM-D total MMSE total GDS total SCAG total PLUTCHIK Total WMS	1] 3.8 (1.44) 2] 3.8 (1.51) 1] 3.7 (0.59) 2] 3.3 (0.77) 1] 13.1 (6.20) 2] 14.4(7.67) 1] 18.4 (5.57) 2] 17.6 (5.47) 1] 4.0 (.79) 2] 4.1 (.83) 1] 53.0 (14.40) 2] 57.5 (15.70) 1] 19.2 (7.14) 2] 20.3 (6.87) 1] 74.9 (16.67) 2] 71.6 (13.19)				1] 3.6 (1.3) 2] 3.2 (1.28) 1] 3.3 (.86) 2] 2.7 (0.86) 1] 12.1 (6.42) 2] 10.4 (5.63) 1] 19.2 (5.74) 2] 21.0 (5.14) 1] 3.8 (.90) 2] 3.5 (.85) 1] 46.9 (14.47) 2] 44.8 (12.79) 1] 17.6 (6.26) 2] 16.9 (7.41) 1] 80.7 (19.07) 2] 85.4 (18.72)	3] <0.018 3] <0.001 3] <0.001 3] <0.001 3] <0.001 3] <0.001 3] <0.013 3] <0.001

EvTable231. Study results: Nimodipine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point:**		**Final: 26w**	
Pantoni, 2000a	ITT Analysis 1] Placebo change from baseline 2] Nimodipine 90 mg/d change from baseline 3] Placebo vs Nimodipine change from baseline	<u>GBS total</u> <u>GBS-i</u> CDR MMSE CGI (item 1) CGI (item 2) FOM (total recall) IADL	1] 0.85 (0.55) 2] 0.88 (0.58) 1] 1.06 (0.65) 2] 1.13 (0.73) 1] 21.46 (4.24) 2] 21.24 (4.07)				1] 0.23 (0.49) 2] 0.85 (0.55) 1] 0.25 (0.58) 2] 0.21 (0.64) 1] 1.16 (0.55) 2] 1.12 (0.60) 1] –0.83 (3.29) 2] –0.87 (3.66) 1] 0.14 (0.61) 2] 0.21 (0.57) 1] 4.02 (1.06) 2] 4.02 (0.99) 1] –2.56 (5.53) 2] –2.28 (6.54) 1] 0.14 (0.39) 2] 0.11 (0.32)	3] 0.67 3] 0.60 3] 0.67 3] 0.94 favours placebo 3] 0.35 3] 0.95 favours placebo 3] 0.67 3] 0.41

EvTable232. Study results: Nizatidine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12m	
Carlson, 2002 Breitner, 1999	ITT Analysis 1] Placebo change from baseline 2] Nizatidine 75 mg bid change from baseline 3] Difference between placebo and Nizatidine change from baseline	COWA Letter fluency Category Fluency Boston Naming test WMS Immediate Recall WMS Delayed Recall Word List Immediate Recall Word list Delayed Recall Constructional Praxis test Constructional Praxis, recall IADL					1] 1.4 2] -0.2 1] 0.5 2] 2.0 1] 1.4 2] 0.6 1] 0.4 2] 2.1 1] -0.8 2] 0.9 1] 1.8 2] 2.1 1] 0.3 2] 0.3 1] 1.6 2] 1.9 1] 1.1 2] 0.3	3] 0.460 3] 0.611 3] 0.231 3] 0.147 3] 0.087 3] 0.413 3] 0.916 3] 0.704 3] 0.224

EvTable233. Study results: ACTH4-9 (Org 2766).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 4w	
Kragh-Sorensen 1986	OC Analysis 1] Org 2766 5 mg vs Placebo 2] Org 2766 20 mg vs Placebo 3] Org 2766 40 mg vs Placebo 4] Org 2766 80 mg vs Placebo	GAGS SCAG total LPRS						1] <0.05 1] <0.01 2] <0.09 3] <0.01 4] <0.01 4] <0.05

EvTable234. Study results: ACTH 4-9 (Org 2766).

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 6m	
Soininen 1985 Partanen 1986 Soininen 1984	OC Analysis 1] Placebo vs ACTH 4-9 (Org 2766)	SCAG AGS-E LPRS McGBRS GPI-E					1] 0.8 CI (-6.8 to 5.1) 1] -0.2 CI (-3.1 to 2.7) 1] 1.2 CI (-3.4 to 5.8) 1] -0.0 CI (-2.4 to 2.4) 1] -0.1 CI (-3.8 to 3.7)	1] NS 1] NS 1] NS 1] NS 1] NS

EvTable235. Study results: Prednisone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 1y**	
Aisen 2000b Aisen 2000a	ITT Analysis 1] Placebo change from baseline 2] Prednisone 20 mg decreasing change from baseline 3] Difference between Placebo and Prednisone in change from baseline	<u>ADAS-Cog</u> CDR-SB BDRS HAM-D BPRS					1] 6.3 (6.4) 2] 8.2 (7.8) 1] 2.2 (1.8) 2] 2.9 (2.5) 1] 1.7 (1.9) 2] 1.7 (2.1) 1] 0.7 (3.6) 2] 1.7 (4.5) 1] 2.0 (6.6) 2] 5.4 (8.2)	3] 0.16 3] 0.07 3] 0.60 3] 0.25 3] 0.003

EvTable236. Study results: Simvastatin.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 26w	
Simons 2002	OC Analysis 1] Placebo 2] Simvastatin 80 mg/d 3] Placebo change from baseline 4] Simvastatin change from baseline 5] Simvastatin vs. Placebo	 MMSE ADAS-cog	 1] 17.1 (4.9) 2] 17.8 (5.0) 1] 33.2 (11.3) 2] 29.4 (10.4)				 1] 14.4 (5.6) 2] 17.2 (4.8) 3] 3.4 (7.0) 4] 4.1 (6.5)	 3] <0.05 4] NS 5] <0.02 3] NS 4] NS 5] NS

EvTable237. Study results: Thiamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 6m		Final: (specify) 12m	
Nolan, 1990	Completers Analysis 1] Lactose placebo 2] Thiamine 3 g/ d 3] Change from baseline across groups	MMSE Verbal Learning Score BNT	1] 16.0 (5.7) 2] 16.6 (5.73)		1] 16.4 (7.7) 2] 13.4 (7.2)	3] <.05	1] 14.6 (7.09) 2] 10.4 (9.13)	3] <0.05 3] <0.05 3]<0.05

EvTable238. Study results: Vincamine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6w**		**Final: (specify) 12w**	
Fischhof 1996	OC Population 1] Placebo DAT 2] Placebo MID 3] Vincamine 30 mg/d DAT 4] Vincamine 30 mg/d MID 5] Vincamine vs Placebo 6] All Placebo 7] All Vincamine 8] Placebo vs Vincamine DAT 9] Placebo vs Vincamine MID	CGI CGI Total Improvement CGI Worse SCAG BGP Need for help SKT	1] 5.0 (0.3) 2] 4.9 (0.4) 3] 5.0 (0.0) 4] 5.0 (0.2) 1] 69.0 (7.4) 2] 70.1 (6.5) 3] 68.8 (7.2) 4] 68.3 (7.0) 1] 15.0 (9.1) 2] 12.5 (9.0) 3] 12.3 (8.8) 4] 12.9 (9.1) 1] 17.5 (3.3) 2] 17.6 (2.8) 3] 17.8 (2.6) 4] 18.1 (2.6)			5] <0.05 5] <0.05 5] <0.05	1] 4.6 (0.8) 2] 4.9 (0.7) 3] 2.8 (1.0) 4] 3.7 (1.1) 6] 25% 7] 72% 6] 7% 7] 3% 1] 67.9 (8.0) 2] 68.1 (7.5) 3] 62.1 (8.5) 4] 63.4 (6.7) 1] 14.2 (9.0) 2] 12.3 (8.7) 3] 10.4 (8.8) 4] 11.0 (8.3) 1] 17.5 (3.6) 2] 17.2 (3.1) 3] 14.8 (4.4) 4] 14.8 (4.4)	 5] <0.05 8] <0.05 9] <0.05

EvTable239. Study results: Piracetam.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify)**		**Final: (specify) 12m**	
Croisile 1993	OC Analysis 1] Placebo 2] Piracetam 8g/d 3] Placebo difference from baseline 4] Piracetam difference from baseline 5] Placebo vs Piracetam	MMSE	1] 19.31(3.32) 2] 19.21 (3.98)				1] 16.4(6.60) 2] 18.10(5.70)	3] <0.05 4] NS 5] NS
		MADRS	1] 5.75(3.45) 2] 9.50(6.82)				1] 7.88(5.68) 2] 10.14(7.61)	3] NS 4] NS 5] NS
		Blessed A	1] 4.28(3.34) 2] 4.96(3.72)				1] 7.72(5.47) 2] 6.46(4.51)	3] <0.01 4] <0.05 5] NS
		Aphasia Battery	1] 1.76(1.94) 2] 1.67(1.75)				1] 6.15(7.68) 2] 3.41(4.88)	3] <0.01 4] NS 5] NS
		Logical Digit Span	1] 14.69(4.21) 2] 12.36(4.65)				1] 10.88(6.16) 2] 11.50(5.37)	3] <0.05 4] NS 5] NS

EvTable240. Study results: Xantinolnicotinate.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify)		Final: (specify) 12w	
Kanowski 1990	OC Population 1] Placebo SDAT subgroup 2] Xantinolnicotinate 1g tid SDAT subgroup 3] Placebo MID subgroup 4] Xantinolnicotinate 1g tid MID subgroup 5] difference between Placebo and Xantinolnicotinate SDAT subgroup 6] difference between Placebo and Xantinolnicotinate MID subgroup	<u>CGI</u> SCAG Decrease in mean value BGP Digit Connection Test Digit Symbol Substitution test					1] 5.6 2] 4.6 3] 5.3 4] 4.5 1] 2.1% 2] 10.1% 3] 1.7% 4] 9.8%	5] <0.001 6] <0.002 7] <0.001 8] <0.001 5] <0.0001 6] <0.0002 5] NS 6] NS 5] <0.001 6] <0.001 5] <0.01 6] <0.03

EvTable240. Study results: Xantinolnicotinate cont'd.

REF ID#	Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify)		Final: (specify) 12w	
		7] Xantinolnicotinate SDAT change from baseline 8] Xantinolnicotinate MID change from baseline							

EvTable241. Study results: Donepezil (DPZ) - Vitamin E.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 3 m**		**Final: (specify) 6 m**	
Thomas 2001	OC Analysis 1] DPZ 10 mg d 2] Vitamin E 2,000 IU 3] change from baseline with DPZ 4] change from baseline with Vitamin E 5] DPZ vs Vitamin E change from baseline	WAIS	1] 72 (2.0)* 2] 72 (2.0)*		1] 74 (2.0)* 2] 72 (2.0)*		1] 75 (2.0)* 2] 71 (2.1)*	3] 0.15 4] 0.43
		MMSE	1] 16 (0.5)* 2] 16 (0.5)*		1] 16 (0.6)* 2] 15 (0.5)*	5] <0.001 favors DZP	1] 16 (0.5)* 2] 15 (0.6)*	3] 0.06 4] 0.07 5] <0.001 favors DPZ
		ADAS-cog	1] 33.34 (2.7)* 2] 33.45 (2.6)*		1] 31.55 (2.7)* 2] 36.09 (2.8)*		1] 31.84 2.7)* 2] 39.07 (2.7)*	3] <0.001 4] <0.01
		NPI	1] 21.9 (0.5)* 2] 21.9 (0.5)*				1] 16.8 (0.2)* 2] 22.8 (1.2)*	

*SEM

EvTable242. Study results: Fluoxetine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 30d**		**Final: (specify) 45d**	
Taragano 1997	OC Analysis 1] Fluoxetine 10 mg/d 2] Amitriptyline 25 mg/d 3] Between treatments	Ham-D MMSE	1] 25.3 (3.8) 2] 26.3 (4.0) 1] 20.0 (3.2) 2] 18.8 (4.2)	3] 0.10 3] 0.10	1] 19.3 (3.2) 2] 17.8 (2.5)	3] 0.10	1] 16.7 (2.9) 2] 15.6 (3.2) 1] 21.4 (2.9) 2] 21.5 (3.5)	3] 0.10 3] 0.10

EvTable243. Study results: 5'-MTHF - Trazodone.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 4w**		**Final: (specify) 8w**	
Passeri 1992	OC Analysis							
	1] 5'-MTHF 50 mg/d	HDRS	1] 23 (5) 2] 23 (3) 5] 23 (5) 6] 23 (4) 9] 21 (5) 10] 23 (3)		1] 20(6) 2] 21 (4) 5] 21 (6) 6] 21 (5) 9] 17 (7) 10] 22 (2)	3] <0.01 4] <0.05 7] <0.01 8] <0.01	1] 18 (6) 2] 19 (5) 5] 18 (6) 6] 19 (6) 9] 18 (5) 10] 20 (3)	3] <0.01 4] <0.01 7] <0.01 8] <0.01 11] <0.01
	2] Trazodone 100mg/d							
	3] 5'-MTHF change from baseline							
	4] Trazodone change from baseline	RVM immediate recall	1] 20 (7) 2] 22 (9) 5] 20 (7) 6] 22 (9) 9] 20 (8) 10] 20 (8)				1] 23 (8) 2] 22 (9) 5] 23 (7) 6] 22 (8) 9] 22 (7) 10] 22 (11)	3] <0.01 7] <0.01
	5] 5'-MTHF subgroup AD							
	6] Trazodone subgroup AD							
	7] 5'-MTHF change from baseline subgroup AD	RVM delayed recall	1] 2 (2) 2] 3 (2) 5] 3 (2) 6] 3 (2) 9] 2 (2) 10] 4 (2)				1] 3 (2) 2] 3 (2) 5] 3 (2) 6] 3 (2) 9] 3 (2) 10] 3 (2)	
	8] Trazodone change from baseline subgroup AD							
	9] 5'-MTHF subgroup MID							
	10] Trazodone subgroup MID							
	11] Trazodone change from baseline subgroup MID							

EvTable244. Study results: Citicoline.

Author Year	Analysis Groups	Outcome s Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 45 d**		**Final: (specify) 90 d**	
Parnetti 1994	OC Population 1] Placebo (Ascorbic Acid 100 mg/d) 2] Citicoline 500 mg/d 3] Posatirelin 10 mg/d 4] Ascorbic Acid change from baseline 5] Citicoline change from baseline 6] Posatirelin change from baseline 7] Posatirelin vs Citicoline change from baseline	GBS Emotional impairment GBS Impaired orientation & memory GBS Impaired ability ADL GBS Depression / Anxiety GBS Impaired attention & motivation GBS Intellectual impairment GBS Motor impairment	1] 1.9 (1.0) 2] 1.9 (1.0) 3] 1.9 (1.2) 1] 2.2 (0.9) 2] 2.2 (1.0) 3] 2.1 (1.0) 1] 1.2 (0.8) 2] 1.4 (1.1) 3} 1.2 (1.0) 1] 1.5 (0.9) 2] 1.5 (0.8) 3] 1.6 (1.1) 1] 2.2 (0.9) 2] 2.1 (1.0) 3] 2.1 (1.1) 1] 2.2 (0.8) 2] 2.1 (0.9) 3] 2.0 (0.9) 1] 1.2 (0.8) 2] 1.4 (1.1)		1] 1.8 (1.0) 2] 1.9 (1.1) 3] 1.7 (1.0) 1] 2.1 (1.0) 2] 2.1 (1.0) 3] 2.0 (1.0) 1] 1.3 (0.8) 2] 1.3 (1.0) 3] 1.1 (1.0) 1] 1.5 (0.9) 2] 1.5 (0.9) 3] 1.5 (1.0) 1] 2.1 (0.9) 2] 2.0 (1.0) 3] 1.9 (0.9) 1] 2.1 (0.9) 2] 2.0 (0.9) 3] 1.9 (0.9) 1] 1.3 (0.8) 2] 1.3 (1.0) 3] 1.1 (1.0)		1] 1.9 (1.0) 2] 1.7 (1.0) 3] 1.6 (0.9) 1] 2.1 (1.1) 2] 2.1 (1.0) 3} 1.8 (1.0) 1] 1.3 (0.9) 2] 1.4 (1.0) 3] 1.1 (1.0) 1] 1.4 (0.9) 2] 1.4 (0.9) 3] 1.4 (0.9) 1] 2.1 (1.0) 2] 1.9 (1.0) 3] 1.8 (0.8) 1] 2.1 (1.0) 2] 2.0 (0.9) 3] 1.8 (0.8) 1] 1.3 (0,9) 2] 1.4 (1.0) 3] 1.1 (1.0)	4] NS 5] NS 6] <0.025 4] NS 5] NS 6] NS 7] 0.038 favors Posatirelin 4] NS 5] NS 6] <0.025 4] NS 5] NS 6] NS 7] 0.031 favors Posatirelin 4] NS 5] NS 6] <0.025 5] <0.025 7] 0.037 favors Posatirelin 5] <0.025

EvTable244. Study results: Citicoline cont'd.

REF ID#	Author Year	Analysis Groups	Outcome s Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
				Baseline		Mid-Point: (specify) 45 d		Final: (specify) 90 d	
			MMSE	1] 16.4 (2.7) 2] 16.5 (2.6) 3] 16.6 (2.5)				1] 17.1 (4.1) 2] 17.6 (3.9) 3] 17.8 (3.4)	4] NS 5] NS 6] NS
			HDRS	1] 13.0 (5.0) 2] 11.4 (4.9) 3] 12.6 (5.0)				1] 11.4 (4.9) 2] 11.3 (5.2) 3] 11.1 (5.3)	4] NS 5] NS 6] NS

EvTable245. Study results: Pyritinol - Hydergine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 6w**		**Final: (specify) 12w**	
Spilich 1996	OC Analysis 1] Pyritinol 600 mg/d 2] Hydergine 4.5 mg/d 3] Between drugs vs baseline 4] Pyritinol change from baseline 5] Hydergine change from baseline	SCAG CETM	1] 27.0 2] 28.0 1] 13.0 2] 14.8		1] 22.5 2] 25.0 1] 17.0 2] 17.8	3] 0.14	1] 16.5 2] 22.0 1] 19.8 2] 17.0	3] 0.008 favors Pyritinol 4] <0.001 5] <0.002

EvTable246. Study results: Sulfomucopolysaccharides - Cytidine Diphosphocholine.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		Mid-Point: (specify) 2w		Final: (specify) 4w	
Cucinotta 1987	OC Analysis 1] Sulphomucopolysaccharides 500 units 2] CDP-choline 1.0g 3] difference between Sulphomucopolysaccharides and CDP-choline	SCAG	1] 35.35(1.32)* 2] 36.00(1.55)*		1] 32.28(1.28)* 2] 35.00(1.38)*		1] 31.61(1.94)* 2] 35.58(1.56)*	3] <0.05 favors Sulphomucopolysaccharides
		NMS	1] 16.71(0.59)* 2] 17.93(0.56)*		1] 16.14(0.54)* 2] 17.80(0.49)*		1] 15.45(0.66)* 2] 18.08(0.71)*	3] <0.02 favors Sulphomucopolysaccharides
		Digit Symbol	1] 44.66(6.84)* 2] 47.41(4.99)*				1] 65.77(9.46)* 2] 52.00(6.44)*	3] <0.05 favors Sulphomucopolysaccharides
		Digit Span	1] 6.72 (0.33)* 2] 5.91 (0.42)*				1] 6.90 (0.34)* 2] 6.25 (0.44)*	3] NS

*SEM

EvTable247. Study results: Sulodexide - Pentoxifylline.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 4m**		**Final: (specify) 6m**	
Parnetti, 1997	OC Analysis 1] Sulodexide 50 mg bid 2] Pentoxifylline 400 mg tid 3] sulodexide change vs baseline	GBS motor impairment GBS intellectual impairment GBS emotional impairmen MMSE	1] 1.64 (0.14)* 2] 1.59 (0.13)* 1] 2.09 (0.09)* 2] 1.98 (0.08)* 1] 2.1 (0.12)* 2] 1.89 (0.1)* 1] 17.6 (0.4)* 2] 18 (0.4)*		1] 1.58 (0.14)* 2] 1.53 (0.14)* 1] 1.88 (0.09)* 2] 1.95 (0.1)* 1] 1.88 (0.12)* 2] 1.9 (0.1)*	3] <0.01 3] <0.01 3] <0.12	1] 1.54 (0.16)* 2] 1.46 (0.17)* 1] 1.79 (0.1)* 2] 1.87 (0.12)* 1] 1.76 (0.12)* 2] 1.75 (0.11)* 1] 20 (0.6)* 2] 20 (0.4)*	3] <0.01 3] <0.01 3] <0.01

*SEM

EvTable248. Study results: Selegiline - Vitamin E.

Author Year	Analysis Groups	Outcomes Measured	Result Value	P Value	Result Value	P Value	Result Value	P Value
			Baseline		**Mid-Point: (specify) 10m**		**Final: (specify) 20m**	
Sano 1997 Thal 1996	ITT Analysis 1] Placebo 2] Vitamin E 1000IU bid 3] Selegeline 5mg bid 4] Vitamin E 1000IU bid + Selegiline 5mg bid 5] Vitamin E 1000IU bid vs Placebo from baseline 6] Selegeline 5mg bid vs Placebo from baseline 7] Vitamin E 1000IU bid + Selegiline 5mg bid vs Placebo from baseline	<u>Event-free survival</u> Event-free survival with MMSE as covariate			1] 79% 2] 86% 3] 60% 4] 80%		1] 40% 2] 51% 3] 60% 4] 49%	5] 0.077 6] 0.087 7] 0.21 5] 0.001 6] 0.012 7] 0.049

EvTable249. Adverse Events: Other agents.

Adverse events (AE) identified in included studies	**ANIRACETAM** Senin, 1991	**ATEROID** Ban, 1991b	**BMY 21,502** Shrotriya, 1996	**CBM 36-733** Danielczyk, 1988	**CHOTO-SAN** Shimada, 1994	**CHOTO-SAN** Terasawa, 1997	**DEK** Cucinotta, 1996	**VASOPRESSIN (DDAVP)** Peabody, 1986	**DENBUFYLLINE** Treves, 1999
Withdrawn (%) due to AE	T: 0 C: 0	T: 1 C: 2	T: 24 C: 9	T: 3 C: 5	T: 3 C: 0	T: 7 C: 3	T: 4 C: 2	T: 0 C: 0	T: 21 C: 16
AE Checklist (Max 5)	3	2	3	4	3	2	3	2	2
None Reported									
Balance									x
Accidental Injury									
Dizziness			x	x					
Falls									
Behavioral	x								
Agitation							x		
Cardiovascular	x	x		NS			x		
Arrhythmia			x	x			x		
Hypotension							x		
Hypertension				NS		x			
Extrapyramidal									
Tremor									
Gastrointestinal		x					x		
Abdominal pain	x								
Constipation									
Diarrhea						x	x		
Dyspepsia			x			x	x		x
Nausea, vomiting	x						x		x
Metabolic/nutritional						x			
Eating disorder									
Weight Change									
Neurological		x	x	x		x			x
Asthenia									
Psychiatric									
Anxiety			x	x			x		
Confusion, delirium			x				x	x	
Depression									
Respiratory				x					x
Cough, cold, infection									
Rhinitis			x						
Other			x				x		x
Aberrant hematology					x				
Fatigue, weakness									
Fever, flu, pneumonia						x			
Headache			x				x		
Hepatic abnormality	x		x			x			
Muscle/joint disorder									
Pain							x		
Rash, skin disorder							x		
Sleep disorder	x								
Urinary disorder				x		x	x		x

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable249. Adverse Events: Other agents cont'd.

Adverse events (AE) identified in included studies	**NIMODIPINE** Ban, 1990	**NIMODIPINE** Pantoni, 2000a	**NIZATIDINE** Carlson, 2002	**ORG 2766** Soininen, 1985	**ORG 2766** Kragh-Sorensen, 1986	**PIRACETAM** Croisile, 1993	**THIAMINE** Nolan, 1991
Withdrawn (%) due to AE	T: 1 C: 0	T: 0 C: 0	T: NR C: NR	T: 0 C: 0	T: NR C: NR	T: 0 C: 0	T: 0 C: 0
AE Checklist (Max 5)	5	4	3	2	5	3	0
None Reported					x		x
Balance							
Accidental Injury							
Dizziness							
Falls							
Behavioral							
Agitation							
Cardiovascular	NS	NS	x				
Arrhythmia	NS						
Hypotension	NS						
Hypertension							
Extrapyramidal		x					
Tremor							
Gastrointestinal	NS	x				x	
Abdominal pain							
Constipation						x	
Diarrhea	NS						
Dyspepsia							
Nausea, vomiting	NS						
Metabolic/nutritional							
Eating disorder	NS						
Weight Change				NS		NS	
Neurological		S	x				
Asthenia							
Psychiatric		x					
Anxiety							
Confusion, delirium							
Depression							
Respiratory		x					
Cough, cold, infection							
Rhinitis							
Other		x					
Aberrant hematology		x		S		NS	
Fatigue, weakness							
Fever, flu, pneumonia							
Headache	NS						
Hepatic abnormality							
Muscle/joint disorder							
Pain							
Rash, skin disorder		x					
Sleep disorder	NS						
Urinary disorder		x					

NR = Withdrawals due to AE Not Reported; + = Dose response effect on AE
x = Reported adverse event/side effect but not tested for significant differences between groups
S or NS = Reported and tested for statistical differences between placebo and treatment group
S* or NS* = Reported and tested for statistical differences between two (three) treatment groups
[ ] = Symptom NOT reported in the paper

EvTable249. Adverse Events: Other agents cont'd.

Adverse events (AE) identified in included studies	**BUFLOMEDIL** Cucinotta, 1992	**CYCLANDELATE** Weyer, 2000	**CYCLANDELATE** Schellenberg, 1997	**GUANFACINE** Crook, 1992b	**HYDERGINE** Spilich, 1996	**HYDERGINE** Thompson, 1990	**VINCAMINE** Fischhof, 1996	**XANITOLNICOTINATE** Kanowski, 1990	**PENTOXIFYLLINE** Parnetti, 1997
Withdrawn (%) due to AE	T:NR C:NR	T: 7 C: 6	T: 9 C: 6	T: 0 C: 0	T: C:	T: 0 C: 0	T:NR C:NR	T: 0 C: 0	T: 7 C: 6
AE Checklist (Max 5)	1	3	3	0	4	1	3	3	2
None Reported	x			x					
Balance							x	x	
Accidental Injury									
Dizziness								x	
Falls									
Behavioral									
Agitation									
Cardiovascular					x				X
Arrhythmia									
Hypotension							x		
Hypertension									
Extrapyramidal									
Tremor									
Gastrointestinal			x						
Abdominal pain									X
Constipation									
Diarrhea			x				x		
Dyspepsia									
Nausea, vomiting			x				x	x	
Metabolic/nutritional		x							
Eating disorder									
Weight Change									
Neurological									
Asthenia									X
Psychiatric									
Anxiety							x		
Confusion, delirium								x	
Depression			x						
Respiratory									
Cough, cold, infection									
Rhinitis									
Other			x			x		x	
Aberrant hematology									
Fatigue, weakness								x	
Fever, flu, pneumonia									
Headache			x					x	X
Hepatic abnormality									
Muscle/joint disorder									
Pain									
Rash, skin disorder								x	
Sleep disorder							x		
Urinary disorder		x							

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EvTable249. Adverse Events: Other agents cont'd.

Adverse events (AE) identified in included studies	**N-ACETYLCYSTEINE** Adair 2001	**GM-1** Ala, 1990	**LYCOSAMINO GLYCAN-OLYSULPHATE** Ban, 1991a	**DESFERRIOXAMINE** Crapper, McLachlan, 1991	**SIMVASTATIN** Simmons, 2002	**POSATIRELIN** Parnetti, 1995	**5'-MTHF (T) TRADOZONE (C)** Passeri, 1993
Withdrawn (%) due to AE	T: 0 C: 0	T: 10 C: 0	T: 1 C: 4	T: 0 C: 0	T: 8 C: 0	T: 0 C: 0	T: 0 C: 0
AE Checklist (Max 5)	2	3	5	3	2	4	3
None Reported							
Balance							x
Accidental Injury							
Dizziness	X						
Falls							
Behavioral	X						
Agitation		X				X	
Cardiovascular		X	X				
Arrhythmia						X	
Hypotension							
Hypertension							
Extrapyramidal							
Tremor						X	
Gastrointestinal			X				
Abdominal pain							
Constipation			X				
Diarrhea	X						
Dyspepsia						X	
Nausea, vomiting							
Metabolic/nutritional	X		X				
Eating disorder				X			
Weight Change				X			
Neurological							
Asthenia							
Psychiatric							
Anxiety							
Confusion, delirium		X				X	
Depression							
Respiratory							
Cough, cold, infection							
Rhinitis							
Other	X		X		X	X	x
Aberrant hematology							
Fatigue, weakness	X						
Fever, flu, pneumonia							
Headache	X	X				X	
Hepatic abnormality							
Muscle/joint disorder	X				X		
Pain		X					
Rash, skin disorder	X	X				X	
Sleep disorder	X	X				X	
Urinary disorder		X				X	

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EvTable249. Adverse Events: Other agents cont'd.

Adverse events (AE) identified in included studies	**PREDNISONE** Aisen, 2000b	**NIMESULIDE** Aisen, 2002	**DICLOFENAC ISOPROSTOL** Scharf, 1999	**INDOMETHACIN** Rogers, 1993	**HYDROXY-CHLOROQUINE** Van Gool, 2001
Withdrawn (%) due to AE	T: 0 C: 0	T: 5 C: 5	T: 46 C: 6	T: 42 C: 30	T: 0 C: 0
AE Checklist (Max 5)	3	5	2	2	0
None Reported					
Balance					
Accidental Injury					
Dizziness		X			
Falls					
Behavioral		X	X	X	
Agitation					
Cardiovascular					
Arrhythmia					
Hypotension					
Hypertension					
Extrapyramidal					
Tremor					
Gastrointestinal		X		X	
Abdominal pain		S	X		
Constipation	X	S			
Diarrhea					
Dyspepsia					
Nausea, vomiting		X			X
Metabolic/nutritional					
Eating disorder					
Weight Change					
Neurological				X	
Asthenia					
Psychiatric					
Anxiety					
Confusion, delirium					
Depression					
Respiratory					
Cough, cold, infection					
Rhinitis					
Other	S			X	X
Aberrant hematology		X	X		
Fatigue, weakness					
Fever, flu, pneumonia					
Headache	X			X	X
Hepatic abnormality	S	X	X		
Muscle/joint disorder					
Pain					
Rash, skin disorder		S			
Sleep disorder					
Urinary disorder	S	X			

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EvTable249. Adverse Events: Other agents cont'd.

Adverse events (AE) identified in included studies	**FLUOXETINE AMITRIPTYLINE** Taragano, 1997	**SULFOMUCO-POLYSACCHARIDES CDP-CHOLINE** Cucinotta, 1988	**DONEPEZIL** Thomas, 2001	**SELEGILINE VITAMIN E** Sano, 1997
Withdrawn (%) due to AE	T: 58 C: 22	T: C:	T: 0 C: 0	T: 0 C: 0
AE Checklist (Max 5)	3		3	1
None Reported			X	
Balance				S*
Accidental Injury				
Dizziness				
Falls				S*
Behavioral				
Agitation				
Cardiovascular				NS*
Arrhythmia				
Hypotension				
Hypertension				
Extrapyramidal				NS*
Tremor				
Gastrointestinal				NS*
Abdominal pain				
Constipation	X			
Diarrhea	X			
Dyspepsia				
Nausea, vomiting	X			
Metabolic/nutritional				
Eating disorder				
Weight Change				
Neurological				NS*
Asthenia				
Psychiatric				
Anxiety				
Confusion, delirium	X			
Depression				
Respiratory				
Cough, cold, infection				
Rhinitis				
Other				S*
Aberrant hematology				
Fatigue, weakness				
Fever, flu, pneumonia				
Headache				
Hepatic abnormality				
Muscle/joint disorder				
Pain				
Rash, skin disorder				NS*
Sleep disorder				
Urinary disorder				

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